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VOLUME 25  
1932

PUBLISHERS  
AMERICAN MEDICAL ASSOCIATION  
CHICAGO, ILL.





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## CONGENITAL MALFORMATIONS OF THE HANDS

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CHICAGO

The difficulties that confront the physician when he attempts to correlate the various congenital deformities of the hand that he has observed are many and perplexing. Since the etiology of some types is still not established, a scientific classification cannot be made at the present time. It may be possible, however, to simplify the picture, coordinate the known facts and marshal the various descriptive terms into some semblance of order.

Lobster-claw hand, ectrodactylism, club hand, brachydactylism, gigantism, hypodactylism and other descriptive terms have a place in the classification, but as knowledge of the etiology and pathologic processes increases, other terms more definitely descriptive and more clarifying in their relation to other lesions should supplant them.

The material used for this statistical study consists of sixty private patients, studied in the hospital. The patients were on the common service of my associates, Dr. Sumner Koch and Dr. Michael Mason, and myself. A much larger group who were seen in consultation, and many of our own patients for whom we judged there was no operative indication have not been included since, as the patients had not been on our hospital service, adequate study and records are not available. A study of our patients and a survey of the literature demonstrate that in large measure the various lesions may be grouped into those showing: (a) hypoplasia and aplasia, (b) disorientation of tissue and (c) hyperplasia. It is also found that these various malformations have a predilection for certain parts of the hand and forearm; roughly speaking, they may be divided into radial and ulnar lesions which may involve either the ulna or radius and their radicles or both in varying degree. One may find, for instance, an absence of the ulna, a reduplication of the ulna with the radius practically normal, an absence of the radius, a fusion or absence of the radial or ulnar carpal bones, a lack of growth of the ulnar or of the radial elements (brachydactylism, brachyphalangism and ectrodactylism), a reduplication of radial or ulnar digits (polydactylism) or a syndactylism of the digits, etc. The mal-

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From the Surgical Department of Northwestern University Medical School.

Chairman's address, read before the Section on Surgery, General and Abdominal, at the Eighty-Second Annual Meeting of the American Medical Association, Philadelphia, June 11, 1931.

formations are not always restricted to the groups mentioned, yet the division is true to form in such a large proportion of cases as not to present insurmountable obstacles to the use of such a simple classification. Variations are noted, however, with sufficient frequency to turn our attention to the study of their possible explanation.

Naturally, the first approach must be through the etiology. Much has been surmised, many hypotheses suggested and a considerable amount of real investigation done without, it must be admitted, answering the question satisfactorily. Much progress has been made, however, in the proof that earlier theories must be abandoned and the establishment of basic principles that show the way to a possible solution. Too often the earlier writers have taken single examples—such as polydactylism or amputations—and have sought a simple explanation of these, overlooking the fact that the case at hand might be complicated by other lesions not permitting of the same explanation, as for example, the common occurrence of polydactylism with syndactylism, partial amputations with syndactylism. In other words, the subject has often not been considered as a whole, for when even a cursory examination is made of any considerable number of cases it is evident that few patients present lesions that are simple clinical entities. One may not presume to say that a single etiologic factor may be found for all congenital malformations; in fact, it seems probable that this is not true. It is certain, however, that some basic factor or factors affect groups of lesions.

The Ahfield theory of amniotic adhesions as the cause of amputations and polydactylism has found wide credence, although there is little to support it. Lineback reported unilateral polydactylism in a 22 mm. fetus. It is manifest that no amniotic band would be capable of splitting the digit of such a fetus. Such an assumption is incompatible also with the fact that polydactylism is generally found on both the hands and feet; that the digits involved are generally the first and fifth, and finally, that the condition is generally hereditary. Every investigator of note has concluded that amputation by amniotic bands, if it occurs, must be very exceptional. Dr. G. L. Streeter recently made an exhaustive study

Among over 8,000 specimens of the Carnegie Collection nine exhibit various stages of this phenomenon (amputation). From a study of these there is no evidence that the process is due to amniotic bands. Apparently structures described as amniotic bands fall into two categories: (a) macerated sheets of epidermis; (b) strands of exuded fibrous tissue originating from localized necrotic areas of the superficial mesenchymal tissues.

The active stage of the phenomenon occurs about the middle of pregnancy and consists primarily of mesenchymal necrosis. It either involves the ends of one or more digits or is limited to an annular area partially or completely surrounding the extremity higher up. If enough tissue is involved, amputation ensues and the stumps heal by granulation. Where the process is more limited a sharp crease is left corresponding to the destroyed area.

The phenomenon is limited to the limb bud tissues and tends to be symmetrical in the sense of involving all four extremities, although the parts affected are usually at different levels.

of congenital amputations which will be published later. The following abstract is quoted from his work:

This is at least an advance. The explanation of the mesenchymal change may be difficult to find, and indeed the process may be open to further study, but it at least definitely removes the amniotic theory from serious consideration. In this connection the experiments of Bagg, to be mentioned later, are extremely interesting.

The atavistic theory of polydactylism and the archipterygial theory of Gegenbaur found spurious support from hasty deductions made on isolated paleologic forms of life. The well known recession of digits in the horse, deer and other mammals, coupled with the fact that in the human foot the smaller toes are apparently also undergoing recession, gave sufficient grounds for the belief that other digits might have been lost. For example, Pfitzner, in a study of 1,500 patients, found that one-third had two phalanges in the little toe, and Hasselwander found that 80 per cent of Japanese had a similar reduction. The predilection of congenital deformities for the ulnar side of the hand further supported the theory. Bardelaben contended that the progenitors of the mammalia possessed seven digits, basing his assumption on the theory that certain mammals, the whale, for instance, has more than five digits. Embryology proves, however, that the sixth digit of the whale appears some time after the typical five digits. Prentiss,<sup>1</sup> and others also, in extensive studies of the embryos of pigs and other mammals, controverted the theory in a convincing manner, and, finally paleontology proves that the forerunners of the mammalia were pentadactylous.

The archipterygial theory of Gegenbaur originated in the discovery in Bavaria in the deposits of the Jurassic period of two specimens of the earliest known bird (fig. 1 *A*). The bones were well preserved. It had reptilian features, teeth in its jaws, long lizard-like tail, claws on three digits—thumb, index and middle fingers—the ring and little fingers being represented by a half made wing. The second stage is represented by the still existing hoactzin (fig. 1 *B*), a bird still found in British Guiana, with an atypical thumb and index finger, the middle, ring and little fingers being a typical wing. The well known bat has an atypical thumb, with the wing made up from the four fingers. However, the studies of Beebe and others show that in the first three weeks of the hoactzin's life there is a marked regression of the digits. These observations that the claw wing is a progression from the amphibian and sequential to a fore extremity rather than a predecessor have relegated the archipterygial theory of congenital deformities to oblivion.

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1. Prentiss, C. W.: Extra Digits and Digital Reductions, *Pop. Sc. Monthly* 68:336, 1906.



The study of human embryos throws some light on the development of the hand as shown by the work of Bardeen and Lewis<sup>2</sup> on the Mall embryos. Lewis shows that by the fifth week the cartilaginous base of the bones is well laid down (fig. 9), the ulna and radius are well formed, but the fingers and wrist are as yet not well differentiated.

The theory of germ plasm origin is suggested by the fact that patients with malformation of one hand so often show involvement of other extremities in similar deformities and that frequently a hereditary history is obtained. Weighty support to this theory is given by the recent work of Bagg, Little, Müller and others, although experimental proof and clinical reports may be presented to show that injury to the buds can occur later.

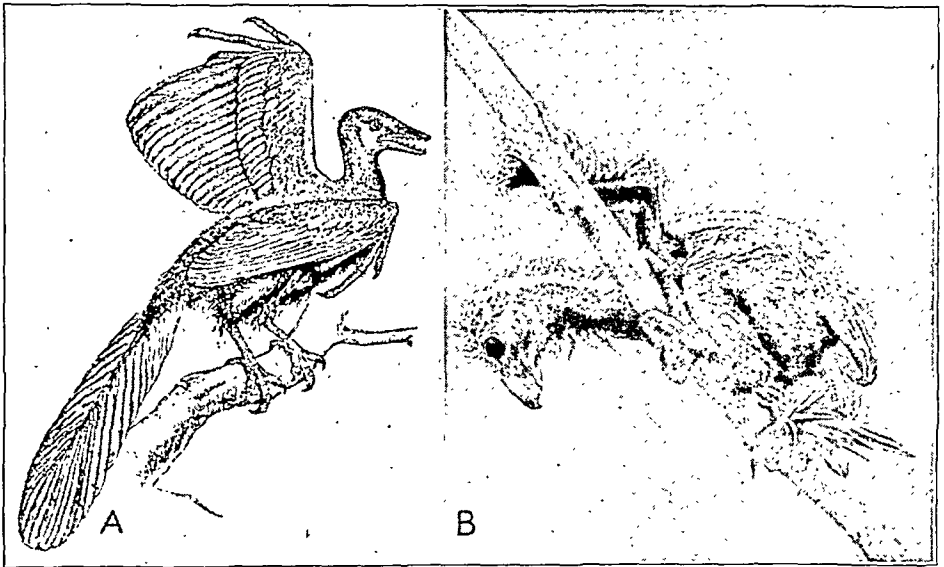


Fig. 1.—*A*, the archaeopteryx. (After William Leche, from J. Arthur Thomson: *Outline of Science*, New York, G. P. Putnam's Sons.) *B*, nesting hoatzin climbing with fingers and toes. (From Beebe, Hartley and Howes: *Tropical Wild Life in British Guiana*, New York, New York Zoological Society.)

The work of Bagg<sup>3</sup> stands out as one of the great contributions to our basic knowledge of this subject. It is great because it proves that congenital deformities may be produced by injury to the germinal cells, that these deformities may be transmitted through succeeding generations, and in that it permits the study of their development throughout fetal life.

2. Bardeen, C. R., and Lewis, W. H.: Development of the Limbs, Body Wall and Back of Man, *Am. J. Anat.* **1**:1, 1901.

3. Bagg, H. J.: Hereditary Abnormalities of the Limbs, Their Origin and Transmission: II. A Morphological Study with Special Reference to the Etiology of Club-Foot, Syndactylism, Hypodactylism, and Congenital Amputation in the Descendants of X-Rayed Mice, *Am. J. Anat.* **43**:167, 1929.

Mice were subjected to x-ray exposure and later bred. Among the congenital deformities appearing were those of some of the extremities. The mice showing this deformity were interbred, and the series followed for nineteen generations with suitable study of control animals. In some the fetuses were removed by operation from the uterus, examined, and in some cases marked and returned to the uterus to be recovered later at normal delivery. Over 5,000 have been studied in the inbred series; 413 had foot defects, 300, club feet with syndactylism; 9, syndactylism alone; 27, hypodactylism; 16, congenital amputations and 93, polydactylism. Out of the study of this rich material has come a knowledge of at least one manner in which these deformities may develop.

Among Bagg's conclusions are the following:

The earliest foot defect is associated with the formation of a blister-like bleb, which raises the epithelium of the foot usually in a localized area. This condition is usually found during the twelfth to the fifteenth day of prenatal life, and is followed by the escape of blood into the bleb and the formation of a localized blood clot. These blood clots may persist until birth (fig. 2).

The extent of the pathological process and its anatomical location determine whether the later-developing foot is to show either congenital amputation, clubbing, hypodactyly, polydactyly or syndactyly.

Polydactyly in my experimental strain of animals may also be an expression of a localized arrest in embryonic development.

Abnormalities of the limbs are definitely inherited. They are recessive to the normal in inheritance. When considered as one of the manifestations of a general tendency to abnormal structure, they approach the Mendelian expectation in behavior.

Valuable as this work is, it leaves unexplained, nevertheless, some of the phenomena of deformities, as, for example, hyperplasia. Nor has it progressed far enough to establish the connecting link between the injury of the germ plasm and the lesion in the bud. Is the process a metaplasia of cells of the part involved or is it secondary to an injury of the vascular or nervous system originating in the germ plasm? One must still speculate as to the factors that lead to injury of the germ plasm in the human embryo, although it has long been a theory that certain toxins may be causative factors. Furthermore, the isolated examples of congenital deformities that seem to have no hereditary history must be explained.

While one stands on rather firm ground as to the probability of most congenital deformities having their origin in the germ plasm, and the work of Bagg suggests the manner in which this occurs in the developing extremity, the known predilection of these deformities for certain parts of the forearm and hand is yet to be explained. The investigations of Lewis on the human embryos demonstrate the early formation of the ulnar and radial buds. The wrist and hand, however, appear but as an undifferentiated end-plate. It is possible that more intensive

study of cell groupings in the wrist and hand in embryos may be of aid, but so far such findings are not available. With two distinct buds in the forearm, ulnar and radial, one can understand how destruction or metaplasia of these primary buds will explain congenital absence, reduplication, deformity and synostosis of the ulna and radius as seen in clinical cases (see figs. 7, 8 and 29). It will also explain the associated changes seen in the hands if one remembers that certain digits are directly or indirectly outgrowths from these two buds. The phylogenetic history of the hand is shrouded in mystery, and one should regard investigations as to the development of the arm of lower forms of life as interesting but by no means conclusive. However, it is interesting to see how easily the deformities of the hand and fingers may be explained if one assumes this phylogenetic history and believes with

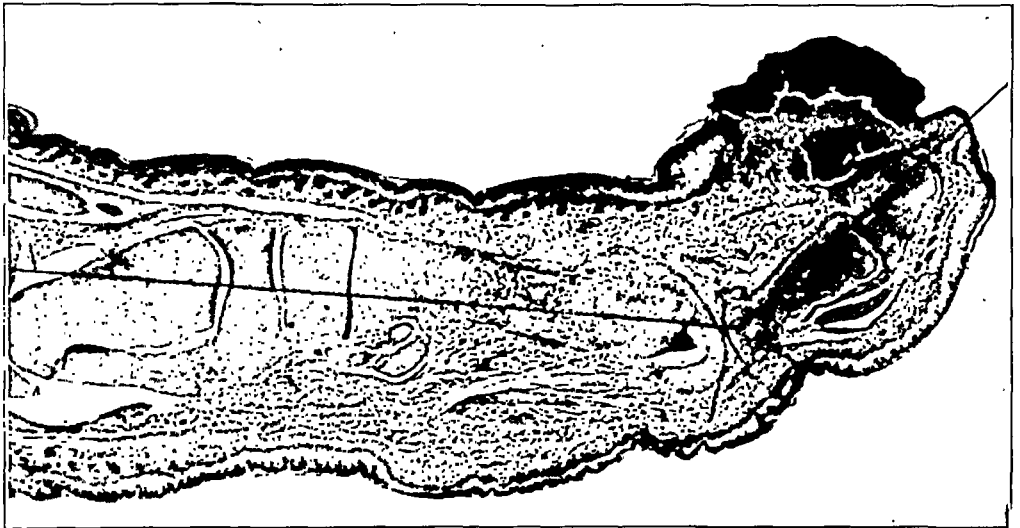


Fig. 2.—Section from the foot of a 1 day old mouse. Note the remnant of an old blood clot and destruction of the cutaneous epithelium. (From Bagg: *Am. J. Anat.* **43**:167, 1929.)

von Baer that "the history of the individual represents the history of the species."

The investigations of Götte and Strasser on Triton larvae, Wiedersheim on Proteus larvae and later investigations on Amphioxus and other low forms of life are suggestive at least. As Goldmann<sup>4</sup> stated, these investigations seem to indicate that at a certain period of its development, the carpus consists of three parallel tissue rays splitting into several parts (carpal bones) from which respectively the "radial" and the "medial" continue into the first two digits. From the "ulnar" ray, which arises secondarily from the ulnar bud, the basal elements of the third digit are derived, and rays accessory and subsidiary to this form the fourth and fifth digits.

4. Goldmann, E. E.: Beitrag zur Lehre von den Missbildungen der Extremitäten, *Beitr. z. klin. Chir.* **7**:239, 1890-1891, 2 pl.

Thus, in the beginning, the first and the second digits are constructed, later the third is formed and still later the fourth and the fifth. If one wishes to introduce ontogenetically the terms "chief" and "accessory rays" which are used in comparative anatomy, one has to consider the rays projecting into the two first digits as chief rays of equal value, while the other fingers together with their carpal elements should be interpreted as lateral accessory buds of the second chief ray with the qualification that the fourth and the fifth fingers are branch buds of the accessory ray passing into the third finger. The schematic drawing presented (fig. 3) illustrates an arbitrary composite picture of the results of these investigations.

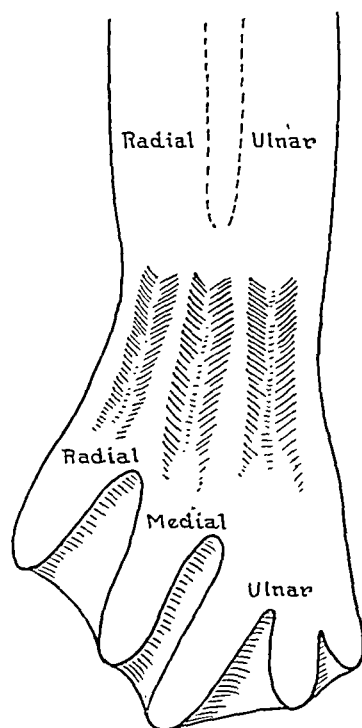


Fig. 3.—Schematic representation of the development of the hand drawn to represent combined observations of Wiedersheim, Götte and Strasser and other investigators.

The thumb originates directly from the radial bud. The middle, ring and little fingers originate from the ulnar bud, while the index lies between the two and may be involved with either in deformities although it is more closely associated with the ulnar bud. Congenital defect of the radius most often involves the thumb alone. In our two cases of congenital absence of the ulna, the thumb and index fingers were both preserved. Herschel claimed that in those cases showing an absence of the radius with a normal hand, one is dealing with a fusion of the ulna with the radius. The thumb separates first from the end-plate; and this is another reason why it is less often involved in a common lesion. The medial bud (index finger) and later that of the third finger

assume independence and must be regarded as more or less equal, while the fourth and fifth represent subordinate buds of the ulnar ray.

The earliest known footprint, that of the *Thrinacosaurus antiquus* found in a slab of uppermost Devonian sandstone, corroborates, according to Professor Lull, the origin of the radial and ulnar sides of the hand from different buds. We are inclined, however, to believe that Dr. Morton's deductions are more probable and that the divisibility of this paleologic foot into two parts is not fully proved. This is discussed in the section dealing with lobster-claw hand. In the living chameleons, this division of the hand into ulnar and radial elements is found.

Our own anatomic and functional studies of the hand support the theory of development as depicted in the schematic drawing (fig. 3). Anatomically, ulnar and radial divisions are found definitely separated by a fibrous partition attached to the middle metacarpal bone.<sup>5</sup> The tendon and tendon sheath of the middle finger are associated with the ulnar space. The index tendon and tendon sheath are associated with the radial space and entirely separated in the palm from the associated little, ring and middle finger ulnar group, but it does become associated with this group at the wrist in a common sheath. The thumb tendon and tendon sheath are completely separated from the four finger tendons and their sheaths throughout their length. This is the exact picture one would expect to find if their origin is that postulated from the embryologic studies mentioned.

A glance at the typical distribution of the vascular and nerve supply supports the assumption that the little, ring and middle fingers are closely associated; that the index finger, though separated, has a closer association with this ulnar group than the thumb.

Functionally, the same picture is seen. The thumb acts independently and the three ulnar fingers together, but in association with the index finger. The proximal flexion function crease on the palm subtends the thumb action, the distal that of the three ulnar fingers and the middle that of the four fingers.

Whether or not this is the true life history of the hand, it is interesting to see that most deformities can be brought into accord with the theory. There is a tendency to certain associated lesions, a predilection of deformities for certain parts of the hand and a predisposition for other parts to escape involvement. For example, the little and ring fingers are most commonly involved together (see figs. 8 and 29). Not infrequently the middle finger joins with them in the distorted picture. Less frequently the index becomes simultaneously affected (see fig. 19). The thumb is seldom involved with the other fingers, and when it is involved the fingers generally escape although at times the index finger joins in the changes (see figs. 7 and 10). In other words, the thumb,

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5. Kanavel: *Infections of the Hands*, ed. 5, Philadelphia, Lea & Febiger, 1925.

index and middle fingers are more liable to individual variations; while the little and ring fingers have a tendency to common involvement frequently in association with the middle finger, less often are the four fingers involved. The not infrequent absence or duplication of the thumb alone is noted in passing; the preservation of the thumb and index fingers in absence of the ulna (see fig. 8); the frequent syndactylism of the lesser fingers, the more common appearance of brachydactylism in the little and ring fingers (see fig. 25); the preservation of the thumb and index finger and the little and ring fingers in lobster-claw hand (see figs. 13 to 18), and the infrequency of lobster-claw hand due to isolated absence of the ring finger. These and other clinical pictures fit the suggested embryologic development of the hand with sufficient accuracy to give a basis for further study, yet one must not assume that the phylogenetic history outlined is a complete explanation of all the congenital malformations of the hand.

In most congenital deformities the hereditary tendency is so well known that it hardly merits discussion. Cushing collected the histories of 302 patients with congenital ankylosis of the proximal and middle phalanges (symphalangism), 25.8 per cent in one family; DeForest Willard reported lobster-claw hand in 15 of 22 children in one family, and in 24 of 80 in another family in three generations; Marshall reported congenital amputation of fingers at the proximal phalanx that ran through four generations; Kellis studied a family of ten generations in which the thumb only was normal, while in all cases other fingers, either two or at least one, showed one phalanx absent; Mohr and Wriedt observed six generations with brachydactylism of the middle phalanx of the index finger. The hereditary nature of syndactylism and polydactylism is too well known to justify comment. The experimental production of hereditary defects in mice by Bagg and Little has already been mentioned. Its presence in other mammals is well known. Stockard and Papanicolaou studied over several years hereditary polydactylism in a strain of guinea-pigs, and they believe that it is inherited as a mendelian dominant. Prentiss concluded from his study on various animals that it is not a recessive characteristic. On the other hand, Brandeis, from a study of polydactylism, expressed the belief that the evidence is not conclusive as to its dominant character, and some things indicate it may be recessive.

While in a majority of cases the evidence seems conclusive that the activating genesis of congenital deformities lies in the germinal cell, yet one must consider the manner in which this activation manifests itself, and whether or not the process may not arise in the buds from other causes than a germinal source.

Here one still falls into the realm of pure speculation. May not a toxin affect either the germinal cell or the cells of the buds? May not the effect be produced through involvement of the vascular system or

the nervous system by direct involvement of these systems in the early stage or their elements in the germ cell or the trophic centers for these systems? The experiments of Bagg postulate a resultant destructive lesion. This does not explain hypertrophy. Hypertrophy of the thumb and index finger alone, of the middle finger to the exclusion of the remainder of the hand and other lesions may have some other explanation. The vague "inherent tendency to growth" and "physiologic growth energy" mean nothing. Valtz thinks that there may be abnormal growth of basic vessel plasm, and the observations of Orlow, von de Rothschild and Brunner seem to support this "osteitis vascularis" as do the pigmentation and hyperemia of the skin in the case of Valtz, although the pigmentation may be due to trophic nerves. Similar pigmentation in partial giant growth has been observed by Wiedermann, Manasse and Grünfeld.

Davida found, in a case of rudimentary development of the forearm and hand, an atrophy of the sixth, seventh and eighth cervical nerve centers and spinal ganglions. Edinger observed similar changes. Strauss<sup>6</sup> found in the entire cervical and dorsal region of a patient with complete amputation of the arm, a relative increase of gray substance, an absence of development in the motor area, a decrease in number and irregular forms of the ganglion cells, dysplasia of the gray commissure, hypertrophy of interstitial tissue and a reduplication of the central canal. There was no especial difference in cross-section from the fifth cervical to the first dorsal so that one could only reason that the whole was a germ plasm change and not restricted to the arm centers. Songuers and Marinesco found in a congenital deformity of the middle finger of the right hand a high grade atrophy of gray substance in the first right dorsal and eighth cervical gray substance near the posterior root with interstitial connective tissue proliferation and atrophy of the cells of the anterior horn. While too much importance should not be attached to these observations, yet they should be mentioned.

Confronted with conflicting theories, confused by the multitude of single clinical observations with overlapping deformities, disturbed by the various and multiple clinical terms that mean nothing etiologically, the clinician is often at a loss to understand the individual case. The investigator also is inclined to study a clinical group rather than a basic phenomenon. We have, therefore, studied the patients presenting themselves in our clinic and gone over the literature of the various case reports to see if we might not develop some simple classification that would serve as a basis for future study. The classification presented is probably far from perfect, but considered in relation to the foregoing etiologic factors it has simplified our understanding of the deformities in the patients we have observed.

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6. Strauss, A.: Case of Absence of Arms in a Child, *J. f. Psychol. u. Neurol.* **36:75**, 1928.

## CONGENITAL MALFORMATIONS OF THE HAND

## A. Moderate Growth Impairment with Disorientation

## Clinical pictures

Hyperplasia  
Polydactylism  
Syndactylism  
Hyperphalangism  
Symphalangism  
Brachydactylism  
Clinodactylism

Radio-ulnar and other synostoses

Mild types of disorientation of any skeletal structures

## B. Severe Growth Impairment with Hypoplasia and Aplasia

## Clinical pictures

Amputations in whole or part  
Phocomelia  
Micromelia  
Hypoplasia and aplasia of radius or ulna and their radicles  
Hypoplasia and aplasia of digits  
Lobster-claw hand

## C. Combinations of A and B

## ANATOMIC DISTRIBUTION OF CONGENITAL MALFORMATIONS WITH EXAMPLES OF CLINICAL PICTURES

## (a) Injury to arm bud

(1) Moderate injury: Radio-ulnar synostosis

(2) Severe injury: Amputation, phocomelia, mirror hands

## (b) Injury to radial and ulnar buds and their radicles: Disorientation or destruction of tissue in whole or part, separately or combined

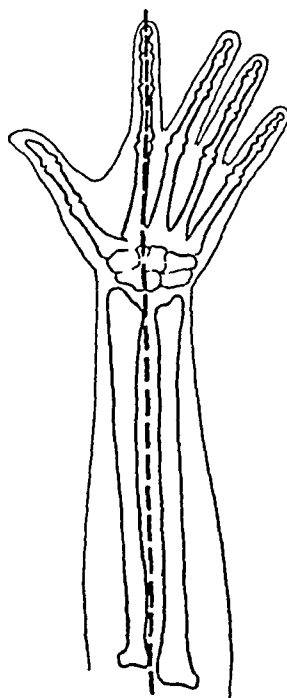
## Radial

## 1. Moderate injury producing disorientation of tissue:

Hyperplasia of thumb  
Double thumb  
Syndactylism, thumb and index finger  
Hyperphalangism of thumb  
Symphalangism of thumb  
Brachydactylism of first metacarpal  
Synostosis of radial carpals

## 2. Severe injury producing:

Aplasia and hypoplasia of radius and thumb in part or as whole



## Ulnar

## 1. Moderate injury producing disorientation of tissue of fingers:

Fingers may present:  
Hypoplasia  
Polydactylism  
Syndactylism  
Brachyphalangism  
Clinodactylism  
Symphalangism  
Hyperphalangism  
Synostosis of ulnar carpals

## 2. Severe injury producing:

Aplasia and hypoplasia of ulna and fingers in part or as whole

Figure 4



This simple classification aids us in the orientation of our cases if it is remembered that while there is the distinct tendency for one or more of these divisions to dominate the picture, yet almost any one or more of the others may be present to some degree. Thus polydactylism, hypoplasia and syndactylism are frequently present in the same patient. The same is true of all the other clinical groups. Hypoplasia in its various forms may be the dominant picture with syndactylism, polydactylism, disorientation of tissue, etc., subordinate. Syndactylism may be the dominant picture with any of the other group subordinate. Furthermore, the radial, medial or ulnar involvement may be dominant with either of the others subordinate in whole or part. Attention is drawn particularly to this at this time so as to avoid continuous repetition of the fact when those various clinical entities are considered that appear frequently enough in a dominant form to merit individual consideration.

Table 1 presents in abstract form the data on our sixty cases.

In the 60 patients used for this study, 84 hands were involved, and these hands presented 121 so-called clinical entities: syndactylism, polydactylism, aplasia, etc. For the sake of clearness, the major clinical entities must be discussed separately, yet it is evident from these figures that they are seldom uncomplicated. The site of injury and the severity of the lesion will determine the major clinical picture. It seems wise at the present time to consider malformations of the hands and draw attention only to the fact that the simultaneous involvement of the legs and various other parts of the body is a further evidence that the source of the deformities lies in the germ plasm. In discussing our various cases, the presence of these associated lesions has for the most part been ignored since we do not wish to complicate the presentation of the subject.

#### HYPOPLASIA AND APLASIA

Hypoplasia and aplasia may be of any degree, from the involvement of the tip of a phalanx to that of the entire extremity. As already mentioned, in the forearm either the radial or ulnar bud or their radicles may be involved, one or the other remaining approximately normal, or both may be involved in varying degrees. The malformation may take the form of absence of a whole or part, so-called amputation, or underdevelopment with the natural form present. An isolated clinical picture may be present or the picture may be one associated with any of the other congenital malformations such as syndactylism, polydactylism or disorientation of tissue.

Certain clinical pictures are so conspicuous that when present they have received undue attention, and the fact that they are but manifestations of the same process has not been appreciated. To these have been given descriptive terms such as amputations; ectromelia,

defective arms or legs; brachymelia, short arm or leg; micromelia, abnormal smallness of part; phocomelia, absence of segments (e. g., humerus, forearm) with the hand attached to the body; hemimelia, absence of the forearm and hand, so-called ectromelia vera; ectrochiria, absence of the hand alone; ectrodactylism, absence of the fingers; brachydactylism, short fingers; brachyphalangism, short phalanges; microdactylism, small fingers; lobster-claw or cleft hand, absence of the medial part of the hand, especially loss of the middle finger and part of the metacarpal. Such terms are not objectionable unless they obscure the fact that they are all but stages of the same process. If the origin of hypoplasia and aplasia is assumed to lie in injury of the germ plasm, it is easy to understand why hypoplasia is so commonly associated with other congenital lesions and is found less commonly than other lesions as a single clinical entity. In other words, syndactylism, and even polydactylism and disorientation of tissue, are evidences of a less severe germinal injury. This is more readily understood if one bears in mind the analogy between these lesions produced by metaplasia or destruction of tissue during embryonal life and the changes seen after severe local infection and abscess formation in later life. In the latter instance, following severe inflammation without mass destruction, one sees disorientation of nerves, muscles and connective tissue with scar tissue formation on recovery. Where there has been mass destruction with abscess formation and surrounding round cell infiltration, loss of tissue at the site of the abscess with surrounding disorientation due to scar tissue is seen on recovery. In congenital lesions with moderate injury, one sees disorientation expressed in syndactylism, polydactylism, etc. With severe destructive injury, one sees hypoplasia or aplasia surrounded by evidences of less severe injury (see fig. 15), syndactylism, polydactylism, etc. In our small group, in 30 hands with hypoplasia, 18 showed syndactylism, 3 polydactylism and 4 congenital anomalies of other parts of the hand. Except in radial hypoplasia, which one would expect not to involve the fingers, there was only one hand uncomplicated by other lesions. Of 52 hands with syndactylism, 19 showed hypoplasia, 12 polydactylism and 4 other anomalies. In 20 hands with polydactylism, 12 showed syndactylism, 3 hypoplasia and 1 other lesions.

In a considerable number of the cases of hypoplasia of limbs, the history showed a hereditary tendency. Moreover, the picture of a given lesion tends to repeat itself in succeeding generations with only slight variations. Almost innumerable examples of this are recorded in the literature. Among these may be mentioned the following: Joachimsthal reported brachyphalangism and hyperphalangism of the index and middle fingers running through several generations of a family; Machal and others, brachydactylism due to a short fourth metacarpal; Mohr

Severe Lesion;  
Hypoplasia;  
Destruction;  
Aplasia

Lower Extremity  
Involved  
L-I-II-III  
R-I-II, both, flap and  
Thiersch graft

L-II-III  
R-II-III

Moderate Lesion; Disorientation

Other Lesions

Polydactylism

Syndactylism

Case 1 L-III-IV, dorsal flap and Thiersch graft

2 L-III-IV, free full thickness graft

3 L-III-IV, free full thickness graft

4 L-II-III, palmar flaps and lateral suture; should have had free full thickness graft

5 L-II-III-IV, proximal flaps and suture

6 L-III-IV, Thiersch graft

7 L-III-IV-V, palmar flaps and Thiersch grafts

8 L-III-IV

9 R-III-IV

10 L-I-II and III-IV

11 R-I-II-III

12 R-II-IV

Uncle, mother's brother, had syndactylism; cousin, son of above, had syndactylism; see case record below; bilateral

13 L-III-IV

14 L-III-IV, practically complete union of distal phalanges with one nail; tendons had common sheath; free full thickness skin graft

15 R-IV-V III-IV L- (father) has history of deformity in varying degrees for some generations; two sisters, one nephew and a cousin

L-V, lateral deviation; small and atrophic

Distal aplasia of IV-V, right

L-I-II-III-IV  
R-I-II, fused; III-IV-V, hypoplastic

Ears distorted; macrochilia of lower lip; appearance is that of impaired intelligence

L-distal IV



TABLE 1.—Data on Sixty Cases:—Continued

Case	Moderate Lesion; Disorientation		Severe Lesion; Destruction; Hypoplasia; Aplasia	Lower Extremity Involved	Other Parts of Body
	Syndactylism	Polydactylism			
25	L—I-II-III, complete R—I-II-III-IV, complete		L—I-II-III; metacarpals normal; I, rudiment; proximal phalanx II, normal; middle phalanx I, absent; middle phalanx II, absent; middle phalanx III, rudiment; distal phalanges I-II-III, absent R—I-II-III-IV; metacarpal normal; proximal phalanx I, rudiment; proximal phalanges of II-III-IV, fairly normal; middle and distal phalanges all absent		
26	L—I-II-III-IV-V, complete soft tissue fusion		L—I-II-III-IV-V; metacarpals I and V, atypical; II-II-IV, normal; proximal IV, phalanges I-II and V, absent; present in III; middle and distal phalanges absent (all)		
27	L—I-II-III-IV-V; II-III-IV-V most marked		L—I-II-III, short; some phalanges probably hypoplastic; no x-ray picture		
28	L—I-II-III-IV-V		L—I-II-IV, rudiments of proximal phalanges only; middle and distal phalanges absent (in this case hypoplasia is the marked picture; syndactylism insignificant, fingers distorted toward defect)		

29	L-I-II and IV-V R-I-II and IV-V	.....	L-III most marked; lies transverse; middle and distal absent; IV, all phalanges distorted; V, distal absent	L-II-III-IV-V, hypoplasia syndactylism	Hypoplasia; stenosis of tear ducts; hair scanty on head
30	L-I-II R-I-II	.....	R-III, all phalanges absent; II, distal phalanx absent L-III, all phalanges lost, metacarpal rudiment present; IV-V, normal; I, normal; II, disorientation R-III, all phalanges lost, metacarpal rudiment present; IV-V, normal; I-II, distorted, but fairly normal	.....	.....
31	R-III-IV L-I-II and IV-V, moderate only III-IV-V	.....	R-II, all phalanges lost; III, all phalanges lost; IV, proximal and middle phalanges distorted L-III, possibly lost with reduplication of IV, but picture not clear; probably all digits present, however	.....	.....
32	R-I-II and III-IV	.....	L-III, absent, also metacarpal; II, distal phalanx absent, middle phalanx rudiment; I, distal phalanx rudiment; V, either hyperphalangism or clinodactylism L-I, normal; II, either reduplication or only two elements present; III-IV-V, absent, ulna absent; all carpals absent; fusion of radius and humerus; rudiment upper end of humerus present	L-normal R-syndactylism	Monrolium
33	L-either syndactylism of II-III or reduplication of II or rudiments of II and III present R-no syndactylism	.....	R-V, possibly hyperphalangism	.....	.....
		.....	R-ulna absent; all carpals absent; metacarpals II-III-IV-V, absent; digits II-III-IV-V, absent; I, normal	.....	.....

Moderate Lesion; Disorientation		Other Disorientating Lesions		Severe Lesion; Hypoplasia; Destruction; Aplasia		Lower Extremity Involved		Other Parts of Body	
Polydactylism						Webbed toes		Right femur short piece only; no fibula on right or left leg	
Syndactylism								Pectoralis major lost	
Case									
34				L-I, rudiment only; V, absent, also metacarpals; no carpal; L-II-IV-V, absent; digits and metacarpals; unciform and pisiform absent; one phalanx of III lost; hypophalangism					
35				L-II-III-IV with metacarpals lost; I-V, distal phalanx lost					
36				L-II-III-IV-V, digits and metacarpals absent; skin rudiments present; I metacarpal absent; unciform and pisiform absent					
37				L-I, distal phalanx absent; II-III-IV-V, digits absent except for rudiment of III					
38				R-I-II-III-IV-V, digits and metacarpals absent; skin rudiments present; carpal present					
39				L-I, distal phalanx absent; II-IV, distal, middle and most of proximal phalanges absent; V, distal phalanx absent					
40				R-I, rudiment of digit only					
41				R-radius epiphysis absent; epiphysal rudiments present					
42				R-radius absent; thumb absent; radial carpal absent; lower end of ulna atypical					
43				R-lower 2/3 of ulna absent; III-IV-V, digits and metacarpals absent; ulnar carpal absent					
44				L-lower 2/3 of ulna absent; III-IV-V, digits and metacarpals absent; II, normal; I, polyphalangism and polydactylism					

45	.....	.....	.....	I—amputation at upper fourth of forearm R—II-III-IV-V, hypoplastic	.....	.....
46	.....	.....	R—I-II, metacarpal brachydactylism	.....	.....	.....
47	.....	.....	R—IV, metacarpal brachydactylism	.....	.....	.....
48	.....	R—V, rudiment L—V, rudiment	.....	.....	.....	.....
49	.....	R—V, rudiment L—V, rudiment	.....	.....	.....	.....
50	.....	L—I, rudiment	.....	.....	.....	.....
51	.....	R—I, polydactylous	.....	.....	.....	.....
52	.....	L—mirror hand present V-IV-III-II-III-IV-V; double ulna; partial reduplication of humerus	.....	I—radius absent; I with metacarpal and carpal absent	.....	.....
53	.....	.....	R—radio-ulnar synostosis I—radio-ulnar synostosis	.....	.....	.....
54	.....	.....	R—ulnar abduction of II-III-IV-V I—same	.....	.....	.....
55	.....	.....	R—Claw-hand appearance as if hypoplasia of muscles supplied by ulnar and median nerves	.....	.....	.....
56	.....	.....	R—III, disorientation of proximal interphalangeal joint; subluxation with connective tissue contracture	.....	.....	.....
57	.....	.....	R—V, clinodactyly L—V, clinodactyly; children have same defect	.....	.....	.....
58	R—III-IV L—III-IV	.....	R—III-IV, distal two phalanges distorted R—V, clinodactyly L—V, clinodactyly; mother and brother have clinodactyly	.....	.....	.....
59	.....	.....	L—II, macrodactyly due to neurofibromatosis	.....	.....	.....
60	.....	.....	.....	Amputation upper fourth of left forearm	.....	Amputation both legs at upper third



and Wriedt, brachyphalangism of the middle phalanx of the index finger in six generations. A particularly high percentage of hereditary histories is found in cases of split hand (lobster-claw hand); Haim found this reported in 27 of 67 cases; in 180 patients with split hand and ulnar ectrodactylysm, Lewis and Embleton found all but 13 to have such a history. The list might be prolonged indefinitely, especially in hypoplastic malformations of the hands. In complete amputation above the wrist or massive involvement of the arm, such a history is less often elicited.

#### AMPUTATIONS

Attention has already been drawn to the fact that the commonly accepted theory that amputations are due to amniotic bands has little support and that the investigations of Bagg and Streeter tend to disprove the theory. That Wilkinson found an amputated foot in the vagina at birth, Fitch a foot, Martin a hand and Vassel a whole arm can be as easily explained as due to an intrinsic as an extrinsic cause. The fact that a history of heredity is seldom found in the case of major amputations is offset by the fact that one frequently finds associated congenital anomalies. For example, Badescu reported an entire absence of the left arm and a part of the scapula with absence of the third to the fifth toes and syndactylism of the first and second toes; Parker reported a bilateral amputation through the humerus associated with a left club foot with syndactylism, the right leg 9 inches (22.86 cm.) shorter than the left due to a defect of the femur and an absence of the fibula and four toes. Amputations of the fingers and parts of the hand have, in a large percentage of cases, some associated lesion involving the remainder of the hand. A survey of our own patients with aplasia (table 1) presents numerous similar examples. Furrows are found in every part of the extremity from the fingers to the arm, and they are not infrequently multiple and may be of any degree from a simple band of scar tissue to deep furrows of constricting scar tissue leading to atrophy or loss of the distal part. They may be present alone or in conjunction with other malformations. Goffe reported a constriction of the right forearm as if from a band, but a malformed left hand was present. Abbe reported an amputation of the distal phalanges of the thumb, index and ring fingers, and at the base of the fingers a deep groove in the skin and a similar groove encircling the palm of the left hand with a similar lesion of the index and middle fingers of the right, without, however, any constricting bands. Bagg demonstrated that these also are due to intrinsic destruction of tissue and not amniotic cords. Aplasia (amputation) of the entire arm may be found. Badescu reported absence of the glenoid tubercle of the scapula as well as the arm; Price, absence of all four extremities up to the glenoid and acetabular cavities. The so-called amputation has

been found at any point throughout the extremity. When it occurs in the humerus there is generally puckered skin only to be found at the tip; when it occurs in the forearm, bizarre positions of the ulna and radius are often seen with other lesions such as synarthrosis of elbow joints and unequal aplasia of the ulnar and radial elements (figs. 5 and 6). At the wrist the lesion loses its appearance of a typical amputation, and most frequently skin rudiments of fingers are found in spite of an entire absence of all intervening tissue.

This same picture may be found throughout the extremity. Thus Dumeril and Barton reported cases in which the arm and forearm were

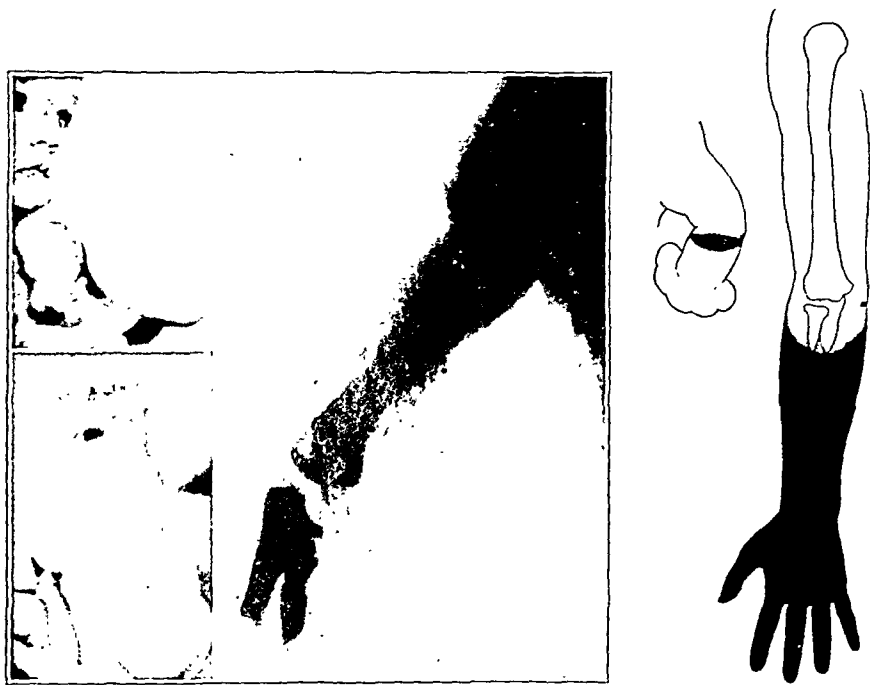


Fig. 5.—Amputation of the forearm (left) and hypoplasia of the fingers (right) with schematic drawing showing the manner of the amputation in case 45.

absent and the hand was attached to the shoulder; Flashlaid, Isenflaum and Stiell, cases in which a rudimentary hand was attached to a rudimentary humerus, the ulna and radius being absent; Chiariello and Bauchard, skin rudiments of fingers attached at the elbow; Levy, Moreau, Aburel and others, rudiments of fingers attached to the forearm or at the wrist. A similar case is illustrated in our series (fig. 6).

One may find the hand and arm well formed with absence or hypoplasia of either or both radial or ulnar elements. The hand may be involved with or without the forearm elements. The lesion is frequently bilateral. Manifestly, the picture is one of aplasia or hypoplasia, and the varied picture is but an expression of the varied intensity and location of the lesion. The hypoplasia may take the

milder form of simple disorientation of tissue. The elbow joint may present lax ligaments with a dislocation of a deformed ulna or radius, deformities of the articular surfaces or synostosis of one or more of the bones with varying degrees of hypoplasia of the ulna and radius and their radicles and the associated soft parts.

Two clinical pictures present themselves conspicuously, and these have been described under the titles, "Absence of the Radius" and "Absence of Ulna." There is some justification for this since the hypoplasia of a radial or ulnar bud does present a typical general picture, although it may vary in the degree of involvement of the part. It should be remembered, however, that there may be overlapping of these two pictures varying with the degree of involvement of the two buds or their radicles.

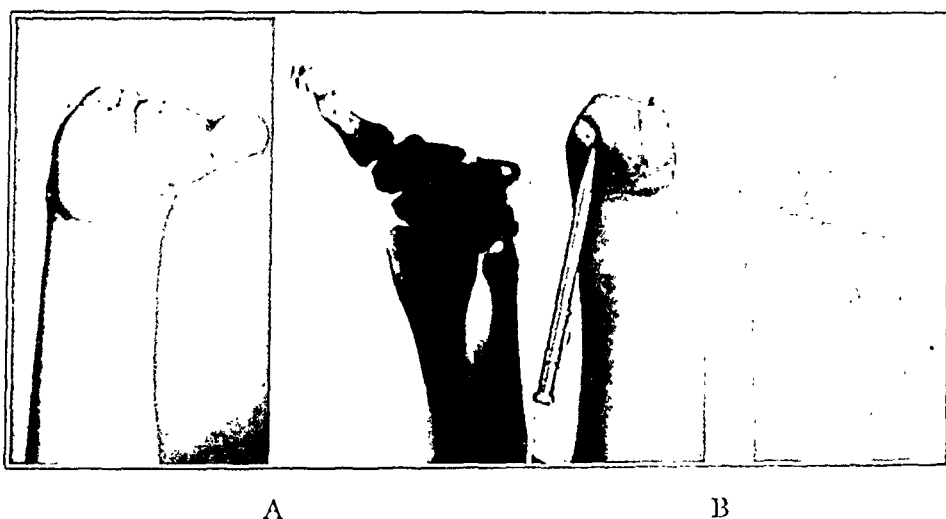


Fig. 6.—Amputations at the carpus with the rudiments of fingers present in cases 37 and 39.

*Absence of the Radius, Radial Hypoplasia.*—Bernacchi reported that in 1,851 patients with congenital malformations, two of four congenital club hands were due to absence of the radius. Tubby alone, however, observed 11 cases and said that he sees about 3 cases yearly at the Royal Orthopedic Hospital in London. Antonelli collected 114 cases up to 1904 and Kato 253 cases up to 1923. In table 2 are analyzed the cases from Kato's<sup>7</sup> admirable contribution.

Four patients with absence of the radius have been observed by us. In one, referred to us by Dr. Boddiger, there was a failure of development of the diaphysis of the radius. The epiphyses were normal, and

7. Kato, K.: Congenital Absence of the Radius; With Review of Literature and Report of Three Cases, *J. Bone & Joint Surg.* 6:589, 1924.

from each of them grew a rudiment about 3 inches (7.8 cm.) long that decreased in size as they approached the center of the forearm. There was some radial deviation of the hand, but no marked clubbing, and function was fairly good. There were no other deformities. A bone graft from the tibia was inserted, impinging on the grooved ends of the two rudiments. This fixed the hand in approximately normal position (fig. 7 *a* and *b*). The healing was satisfactory, and when the patient was seen some months afterward the result seemed entirely satisfactory. Unfortunately, the patient was lost sight of and no subsequent x-ray pictures could be secured. This patient represented one of the smaller groups of these cases, that of diaphyseal hypoplasia. A roentgenogram of the second patient's arm is shown in figure 7.

In general, we find one of four types: (*a*) complete absence of the radius, (*b*) a rudiment of the upper end with more or less of the dia-

TABLE 2.—*Analysis of Two Hundred and Fifty-Three Cases by Kato*

	No. of Cases	Percentage
Bilateral, complete absence of the radius.....	107	46.1
Unilateral, complete absence of the radius.....	98	38.8
Right .....	53	21.5
Left .....	34	13.5
Not stated .....	11	4.7
Bilateral partial absence.....	4	0.8
Unilateral partial absence.....	28	11.1
Right .....	10	4.4
Left .....	16	6.3
Not stated .....	2	0.4
Bilateral mixed, one side complete, other partial.....	4	0.8
Males .....	104	40.9
Females .....	63	25.0
Not stated .....	86	34.1

physis present, (*c*) a rudiment of the lower end with more or less of the diaphysis present and (*d*) absence of the diaphysis.

The commonest type is, as shown in table 2, complete absence of the radius or at least the presence of only a small rudiment of the upper end of the radius. The uncommon types are those in which the diaphysis or upper end is absent.

The upper rudiment, if present, is frequently ankylosed to either the ulna, the humerus or both. The ulna is usually thickened, short and curved generally toward the radial side. A double ulna was present in two cases. Hypoplasia of its upper or lower end may be found, e. g., absence of the olecranon or styloid process. The humerus often presents anomalies at the distal end, which may be broad, rudimentary or even absent. In the carpus the radial bones are often absent or atypical in form. The trapezium and scaphoid are frequently absent, the trapezoid less often. While any or all the bones may be absent, such an extensive lesion is very uncommon. In many instances, however, various carpal bones are noted as atypical in form. The thumb

metacarpal is very frequently absent; the others are generally present. Among the digits, absence or rudimentary form of the thumb is to be expected. In our review of the cases, in which we noted all the hands involved, we found an absence of the thumb and its metacarpal in 32 instances, absence of the thumb alone in 72 and a rudimentary thumb in 14. The fingers are generally normal; a rudimentary index finger was noted twice, and it was absent in 8 cases. The fifth metacarpal was absent once. A double thumb was reported twice, and once it was noted that the thumb had three phalanges. Syndactylism was present in 5 cases, polydactylism exclusive of the thumb in 2. It is thus seen that the typical picture in the patients with extensive involve-

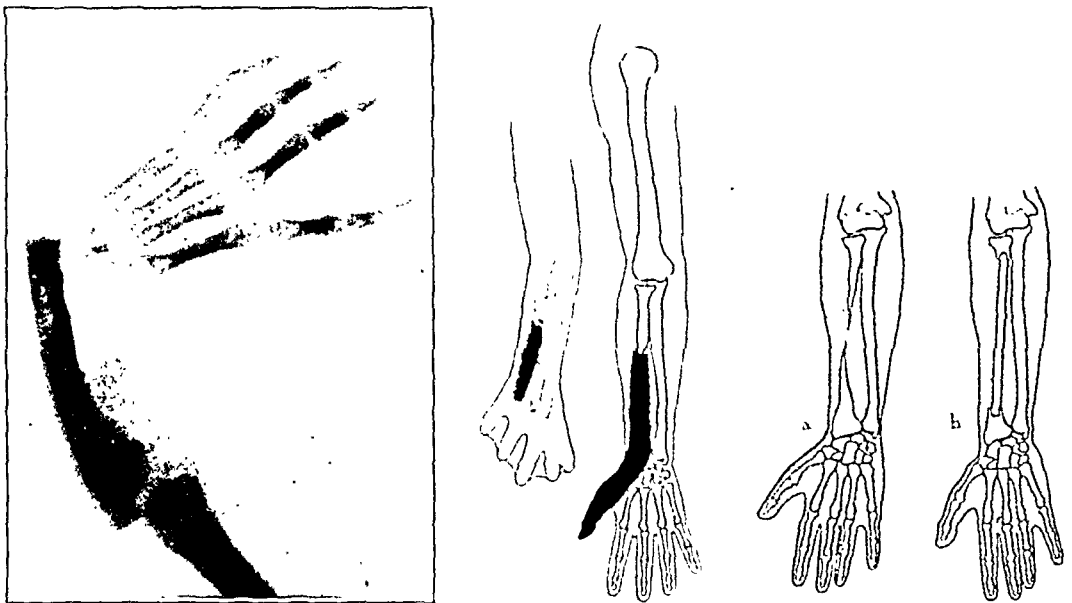


Fig. 7.—Absence of the radius in case 43. Schematic drawing showing the manner of production of radial aplasia. Aplasia of the diaphysis of the radius with a sketch of the operation performed in case 42.

ment is that of a fairly normal hand with an absence of the first metacarpal and the thumb.

The not infrequent ankylosis of the bones at the elbow joint has been noted. There may, however, due to aplasia of both the radius and the head of the ulna, be an abnormal mobility or bizarre positions.

The scapula and clavicle are at times distorted.

As regards the muscular system, it is not uncommon to find an absence of the most radial muscle bodies, or they may be disoriented, fibrosed and contracted. The biceps is often absent, while the pectoralis major and the deltoid, in common with other muscles, may be disoriented or have abnormal insertions. The radial artery is often absent, and in the forearm the radial nerve terminates in many instances at the

elbow and the musculocutaneous nerve is frequently missing. The other arteries and nerves may be disoriented.

Malformations of other parts of the body are usually present such as club foot, cleft palate, strabismus, spina bifida, anomalies of the ear and of the genital organs. Such variation naturally presents many clinical pictures: a typical picture, however, is one in which one sees general atrophy of the arm, the shoulder often small, the upper part of the arm usually fairly normal, the forearm short and distorted and curved with the convexity on the posterior side. The hand shows radial deviation, often at a right angle to the forearm, called by Bouvier "radiopalmar variety of club hand." In severe cases the medial surface of the forearm may be in contact with the hand. The hand is often small, with the thumb absent or with a rudiment loosely attached. In spite of the atrophy and distortion, the function is often surprisingly good. The articulations are generally normal, but movement is restricted because of the luxations and muscular contractures.

A hereditary tendency has been noted in some case histories, but is apparently not common. Blencke reported the condition in four children in one family, and Joachimsthal, similar deformities in a mother and five children.

**Treatment:** The function of the arm and hand may be improved in many of these patients by bone transplantation designed to correct the deformity and secure stability. The principles on which such operations must be carried out are: (a) Severance of fibrous tissue or contracted muscles holding the hand in an atypical position. (b) Insertion of bone either from the ulna or other bones so wedged to the ulna and the carpal bones as to hold the hand in a functioning position. Such transplants must be inserted so that the ends come in contact with denuded bone so as to favor bone growth since the simple insertion of a graft among the muscle bodies on the radial side will end in the absorption of bone. (c) Fixation of the hand in a functioning position with subsequent physical therapy continued for a number of months to restore mobility to distorted joints and function to atrophic muscles. (d) Fixation of the hand in dorsiflexion in certain cases with abnormal motion due to aplasia of the joints so as to place the hand in the position of function. In those cases in which such fixation may ensue, although not sought for, the dressing of the hand should be so applied as to maintain this position if such a result should unexpectedly ensue.

Historically, it may be mentioned that tenotomy of contracted muscles, arthrodesis of the ulnocarpal joint, simple osteotomy of the ulna followed by overcorrection (Hoffa), cuneiform osteotomy of the lower end of the ulna accompanied by section of contracted muscles (Romano), osteotomy of the ulna followed by stretching by adhesive plaster tension followed by resection of the os magnum and the uncinatæ and the inser-

tion of the lower end of the ulna into the cavity, the styloid having been removed (Sayre and Roswell Park), and attachment of the cut end of the ulna to the curetted semilunar with tenotomy (McCurdy) have all been carried out with only moderate success.

Bardenheuer and Antonelli have split the ulna and used the radial fragments as a substitute for the radius. In certain cases with large ulnae, this procedure may have some advantages.

Bardenheuer, followed by Tubby, split the distal end of the ulna into radial and ulnar portions and pushed a carpal bone up between the lower ends. The ends of the ulna and the new radius were fastened to adjoining carpals by an ivory peg. If the upper end of the severed fragment is permitted to remain attached to the ulna, this operation should be followed by fair success. If, however, it is completely detached, absorption is likely to ensue.

With the idea of creating a new radius separated from the ulna by muscular bodies, Antonelli split the ulna from the distal to near the cubital end, being careful to preserve intact the lower end so as not to produce ankylosis. The middle third of the ulna was then broken obliquely, and the end of the newly formed radius was attached to the ulna and carpus by wire. In a later case, he supplemented this with a plastic operation by means of a Z-shaped incision on the contracted tendons. This procedure also must be limited to a few cases in which an exceptionally large ulna is present.

The second type of bone transplant, that in which the graft is taken from a distance, is illustrated by the patients operated on by Albee, Ryerson and ourselves.

Attention has already been drawn to the fact that in our patient we supplied the diaphysis of the radius by a tibial graft (see fig. 7). The upper and lower ends of the radius were present, so that after cutting off the tapering bone and chiseling out a cavity at either end, the graft was inserted between the two ends and fixed in position by catgut sutures. No muscles were missing, so that after cutting the contracting fibrous bands we had no difficulty in inserting the graft between the muscle bodies although we could not identify accurately the individual muscles. We did, however, divide them grossly into volar and dorsal masses. The bony union of the graft with the remnants of the radius was favored by a collar of periosteum taken from the tibia and wrapped about the junctions of the shaft with the rudiments. As has been stated, at the time last seen some six months after the operation, the result was entirely satisfactory. The position of the hand was improved, unnatural mobility had been corrected and the function was excellent. Unfortunately, the patient was then lost sight of so that the ultimate result cannot be stated.

Albee, in a patient with entire absence of the radius, inserted a tibial graft in its place. This graft was mortised into the ulna at about its

middle and the lower end into properly prepared orifices in the carpus. A similar procedure was carried out on the other side, followed later by an osteotomy of the ulnae to correct ulnar deformity. The tissues were stretched, and an attempt was made to produce overcorrection. This patient had a high degree of radial club hand and great disability. Some years afterward, Dr. Albee had an opportunity to examine the patient.<sup>8</sup> The result was excellent. The patient could play tennis, drive a car, paint, etc., and roentgen examination showed a firm fixation and growth of the graft.

In a second case in which the carpus was missing the graft was mortised into the first metacarpal, and the proximal end was placed among the muscles at the elbow. The same intermuscular position of the upper end was used in a third case. It is to be feared that the two last operative procedures will not secure the excellent result of the first since they violate the principle that both ends of the graft should lie in contact with bone where possible, otherwise more or less absorption of the graft is likely to ensue. Ryerson, in his case, placed his whole graft intermuscularly, leaving the periosteum and distal epiphyseal cartilage attached to the graft. Here subsequent x-ray pictures showed the absorption of the bone that experience has taught us to expect with such transplants.

*Absence of the Ulna, Ulnar Hypoplasia.*—Absence of the ulna in whole or parts is found less often than absence of the radius. As already stated, Kato collected 253 instances of absence of the radius up to 1923. While we have made no attempt to make a complete collection of case reports of absence of the ulna, yet in a fairly adequate review of the literature we have found only slightly over 50 cases. In 45 of these, including our 2 cases, the case reports are sufficiently descriptive that some conclusions may be drawn as to the general picture found in this lesion.

It is interesting to note that this picture is almost an exact complement of that already described under radial hypoplasia (absence of the radius). Its complementary similarity is expressed in the short forearm, curved radius, atrophy with ulnar deflection of the hand and loss in varying degree of ulnar elements. It may be said, however, that it differs in the fact that dislocation at the elbow is more common and the destruction of digits, metacarpal and carpal elements, is greater. The ulnar deflection is not so conspicuous as is the radial deflection in absence of the radius, but the loss of function is greater due to the fact that there is so often greater destruction of hand elements. This is well illustrated in the photographs of our two patients. It was seen

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8. Albee, F. H.: Formation of Radius Congenitally Absent; Condition Seven Years After Implantation of Bone Graft, *Ann. Surg.* **87**:105, 1928.



in the Miller-Kraft case (fig. 8) that the lesion was bilateral, the lower two thirds of each ulna was lost, the radius was curved in the radial and dorsal direction, was thick and distorted and the upper end had been dislocated to the volar surface of a distorted lower end of the humerus. Only two digits, probably the thumb and index finger, were present on the right side, and there was a probable absence of all metacarpals with only three carpals present which we would hesitate to identify. On the left side were two well formed digits, probably the thumb and index finger with a reduplication of the index finger. There was fair function present in these digits. In the Rossi case the disability

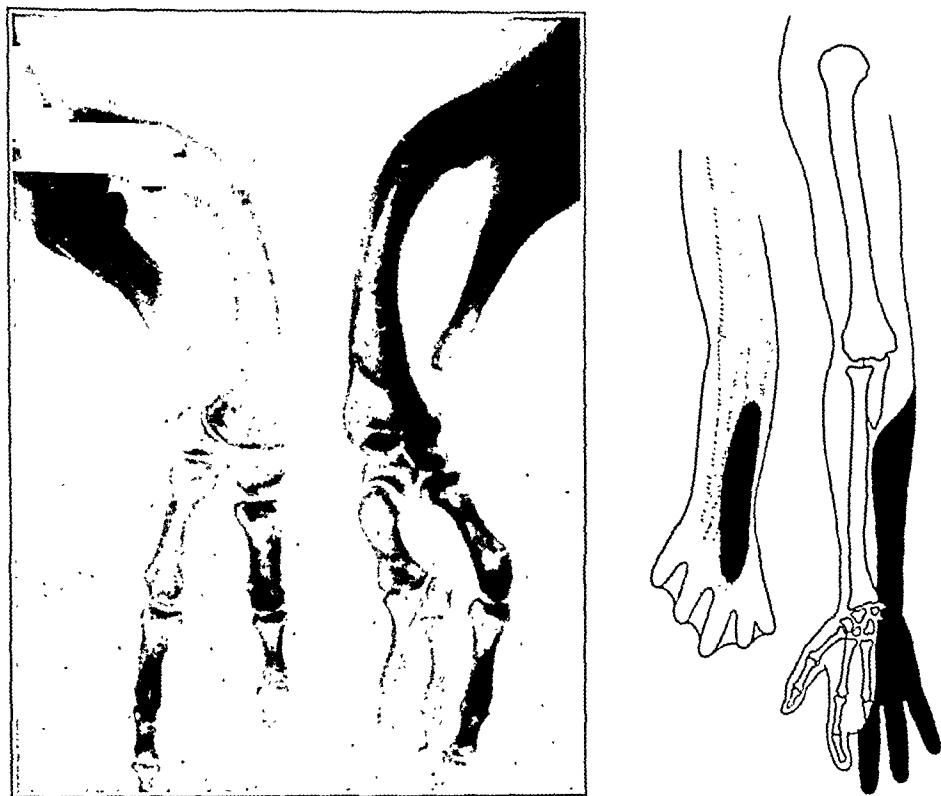


Fig. 8.—Absence of the ulna, ulnar carpals and three ulnar digits and polydactylism of one thumb in case 44 (courtesy of Drs. Miller and Kraft). Schematic drawing showing the manner of production—necrosis of the embryonal ulnar element surrounded by disorientation.

was greater. On the right side the radius was dislocated anteriorly and laterally, not so markedly deformed as in the previous case. There were a small ulnar rudiment, two metacarpals and the rudiment of two carpals. Of the two digits, one was evidently the thumb, the other possibly an index finger with rudiments of reduplicated index phalanges bound to it in syndactylism. On the left side the upper end of the radius was ankylosed to the humerus, and an unidentified single digit with its metacarpal was dislocated to the dorsal surface of the lower end

of the radius. In this case, on the right side the x-ray picture of the forearm bone was inconclusive, but by palpation the bone lay evidently on the radial side, and the presence of radially lying digits, one evidently a thumb, made us conclude that the bone lost was the ulna. Moreover, the loss of so many digits with the carpals and metacarpals is seen more often in absence of the ulna than in absence of the radius. In these hands the disability is great.

While the data on the 45 cases we have had at our disposal are often incomplete, a study of them does give a fairly accurate idea of the common findings. In 15 of these 45 patients, the lesion was bilateral. In the 60 hands there was practically total loss of the ulna in 23, the upper part was lost in only 1 and the lower part in 18; the diaphysis was absent with both ends present in 3 and both ends were lost and the diaphysis present in 1. It is noted in 9 that there was ankylosis of the radius to the humerus, and in 15 there was a dislocation of the radius upward. Its position in relation to the humerus varied. When the destruction of the ulna was not great, the hand was intact and the function excellent. In 33 hands, however, and possibly more, a loss was noted, varying with the intensity of the destructive lesion.

Absence of the carpal bones was a conspicuous part of the picture. In six it was noted as practically complete. In almost all instances of partial loss it was the ulnar bones that suffered, either the cuneiform and pisiform or the cuneiform, pisiform, uncinatè and os magnum. The trapezium is noted as lost in 1 case. However, a glance at the x-ray pictures of the cases here presented will demonstrate how difficult it is to say more than that ulnar or radial bones are lost, and sometimes it is difficult to be sure of this, but that the loss of the ulnar carpals is the common accompaniment cannot be questioned. Digital and metacarpal loss are found to be what one would expect when the embryologic data and the ontogeny of the hand as discussed under etiology is remembered. One would expect to find a conspicuous involvement of the third, fourth and fifth digits and at times the second, while the first (the thumb) would be expected to escape. In the 33 hypoplastic hands, the loss is as follows: the second, third, fourth and fifth digits, 6 cases; the third, fourth and fifth, 11 cases; the fourth and fifth, 11 cases; the second and fifth, 2 cases; the fourth, 1 case, and the fifth, 1 case. The character of the digital loss is more graphically shown in classifying the loss of individual digits: loss of the fifth digit, 32 cases; the fourth, 29 cases; the third, 18 cases; the second, 8 cases; the first, 4 cases; but in 9 it was noted that the thumb showed some pathologic change, e. g., syndactylism, loss of phalanx, symphalangism. This marked predilection for extensive destruction of the ulnar digits stands out in sharp contrast with radial hypoplasia in which over a hundred hands showed involvement of the

thumb with the remaining digits normal in almost all cases, except that the index showed distortion in several cases. The discrepancy in the statistics arises from inadequate histories.

As to associated lesions, the lower end of the humerus is frequently atypical and may be short. Club foot, deformity of the scapula and absence of the fibula, patella and tibia are noted at times. Absence of the ulnar artery and nerve is not infrequent, as is also loss of the flexor carpi ulnaris and some of the muscles of the hypothenar area. Muscular atrophy is common. Syndactylism appears frequently and polydactylism at times; bifid pollex was noted twice.

We therefore portray the clinical picture as follows: The lesion is frequently bilateral, the arm often short, the elbow greatly distorted with the radius dislocated upward, the forearm short, not much flexed on the arm, atrophic, with a slight curvature to the radial and often the dorsal side. The hand, if present, is commonly in moderate ulnar deflection lying between supination and pronation (ulnar club hand, Stoffel, Stempel), but generally with good function. When the hand is involved there is often great loss including the carpals, metacarpals and digits, the maximum loss being on the ulnar side, often only one or two radial digits being present, and these with little function and not infrequently showing syndactylism. Congenital malformations may be present in other parts of the body. A hereditary history is not often found.

Treatment: When the hand is intact, the function is often so excellent as not to demand surgical intervention. With considerable loss of the ulna, however, arthroplastic procedures may be demanded at the elbow to secure mobility, although we are not aware that this has been done. Cases may also be found in which a transplant of bone may be necessary to secure stability and function. This, however, will occur in only the exceptional case, since if there is a functioning hand the deviation and distortion is not so great as in radial loss; moreover, in the case with extensive loss the hand is so often badly crippled that the restoration of the ulna will not secure a satisfactorily functioning hand. If such a procedure is carried out, it should follow on the same lines as described for restoration of the radius. At times the treatment of the syndactylism or the removal of rudimentary elements in the hand may be advisable to increase function. We, however, have had no case in which we believed surgical intervention would improve the function.

#### HYPOPLASIA OF HAND

Attention has already been drawn to the rather typical pictures of ulnar and radial hypoplasia in various parts of the hand which arise sequentially to a lesion in the forearm.

When one considers hypoplasia in the hand arising from a lesion primarily affecting the hand, one would not expect to find a few typical lesions, but rather a multiple of pictures arising as a result of the varying locations, degrees of involvement and periods of embryonic life at which the insult occurred. If the lesion involves the proximal part of the hand or wrist, the whole hand may be lost; if the lesion is lateral, it may be the thumb alone or any radial group or the ulnar group in part or whole that is involved. If the lesion is extensive and below the origin of the thumb, the fingers may all be involved, the thumb escaping injury; if a smaller median lesion is present the medial digits only will be affected, the lateral being normal, or finally there may be involvement of single digits in whole or part. Not only this, but the individual bones may be involved, the hand as a whole being normal. These bones may be absent or fail of proper growth (brachydactylism, brachyphalangism, absence or hypoplasia of carpal bones, etc.). Certain of these lesions have been singled out for special consideration because of the conspicuous nature of the lesion or of its frequent isolated appearance, e. g., absence of the thumb, defect of the median group of phalanges (split hand or lobster-claw hand), brachydactylism and brachyphalangism. Again it should be emphasized, however, that they are but phases of the same general process. The ontogeny of the hand, however, predisposes to certain groupings of the lesions. Due to the development of the thumb from an isolated bud it is not uncommon to have a hypoplastic thumb with the remainder of the hand normal and hypoplastic fingers with a normal thumb. Since the little finger is an accessory bud twice removed from a primary bud and is terminal, the blood supply is easily interfered with so it also is subject to exceptionally frequent involvement. The close association of the middle, ring and little fingers in embryonal life determines the frequent association of these in a hypoplastic process.

The various types of hypoplasia of the hand have certain things in common. The picture is very seldom that of hypoplasia alone. The involvement of more than one extremity is very frequent and sometimes all are involved in more or less similar lesions. A hereditary history is very common.

The associated lesions are many and varied in type and degree. One would expect this when it is remembered that a lesion leading to destruction would have around it an area of disorientation of cell growth. A similar picture is seen in an abscess where there is a local destruction of tissue surrounded by an area of cellular infiltration with ultimate scar tissue formation and structural deformity. The same process occurring in embryonal life before structural formation would certainly lead to disorientation of the developing tissue about the area of destruction

(see fig. 14). Syndactylism and polydactylism are especially common. Symphalangism, polyphalangism, brachydactylism, brachyphalangism and disorientation of tissue all appear. Any or all of these may be present in an individual case.

This association of various lesions is illustrated in our cases. In 30 hands showing more or less hypoplasia there were 18 with syndactylisms, 3 with polydactylisms and 4 with disorientation of tissue, or 55 various lesions in the 30 hands.

The hereditary nature of the lesions involving the hand alone is so conspicuous that it merits no further discussion than that already given.

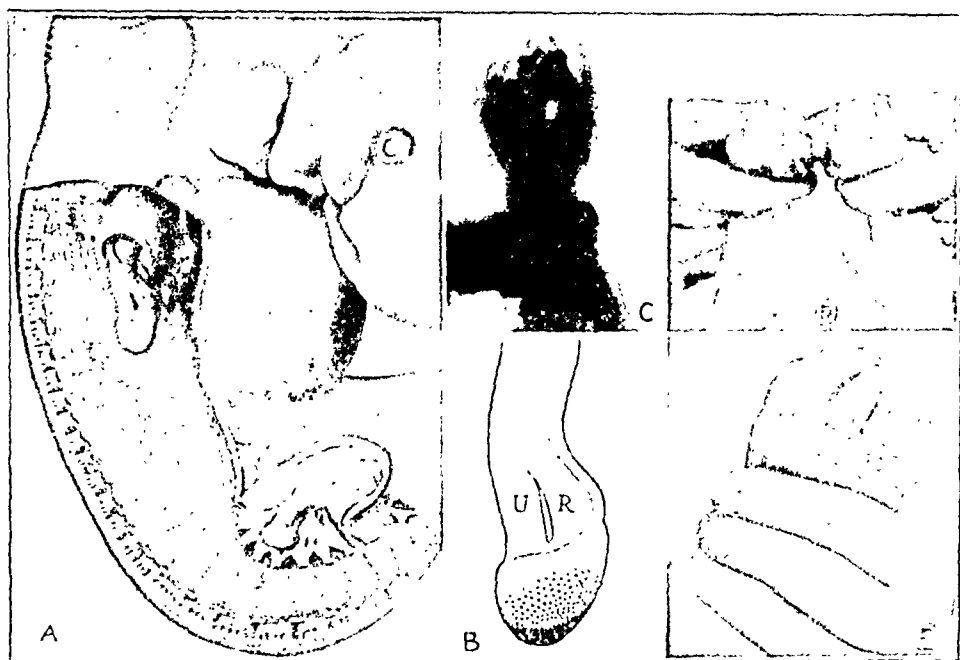


Fig. 9.—*A*, embryo (Mall) of 4 weeks, showing ulnar and radial development with undifferentiated end-plate (hand and fingers). (From Bardeen and Lewis, *Am. J. Anat.* 1:1, 1901.) *B*, enlarged drawing of the ulna and radius with end-plate showing schematic distal disorientation. *C*, *D* and *E*, photographs of the hands showing result of such disorientation in cases 21, 22 and 23.

These general remarks are probably best illustrated by a short résumé of the findings in some of the patients who have come to us presenting hypoplasia of the hand as a major clinical sign.

*Hypoplasia of All Elements.*—CASE 39.—Miss Z., referred by Dr. Pavlik (see fig. 6 *B*), had unilateral aplasia of the hand, but showed no other congenital malformations. An examination of the x-ray picture discloses an entire absence of the metacarpals and phalanges except for a rudiment of the thumb. The carpal bones seem to be intact, and from the x-ray picture one might assume it to be an amputation by an extrinsic lesion. The photograph of the hand, however, discloses skin rudiments of the digits, the first and fifth being especially noticeable.

CASE 23.—M., described as one of the patients with syndactylism (fig. 9, C, D, E), illustrates the type in which the terminal phalanges of all five digits are hypoplastic, the remainder of the hand being well developed except for the syndactylism.

*Lateral Hypoplasia.*—Complete ulnar hypoplasia is well illustrated by case 37, that of Miss E. in which there was entire absence of all metacarpals and phalanges of the fingers (see fig. 6 A). There was, in addition, a loss of the distal and part of the proximal phalanx of the thumb with some disorientation—fusion of the trapezium and trapezoid—present in the carpus. Again, however, the photograph of the hand shows skin rudiments of the fingers. There was function, though restricted, in the thumb.

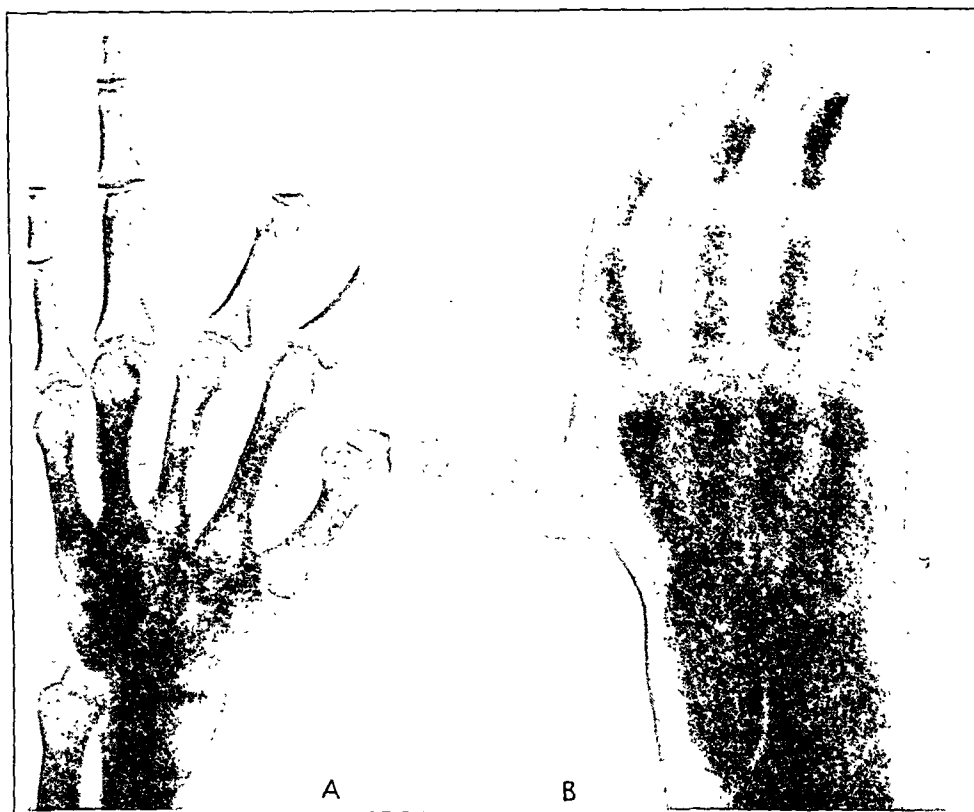


Fig. 10.—Radial hypoplasia in cases 25 and 41.

Another patient (see fig. 29 C) showed hypoplasia of the four ulnar digits, a loss of the distal phalanx and part of the middle phalanx of the index finger, loss of the two distal phalanges and part of the proximal phalanx of the middle and ring fingers, loss of the distal phalanx and symphalangism of the middle and proximal phalanges of the little finger. The thumb was normal with complete function; the hand otherwise normal. This picture begins to merge into that of hypoplasia of the middle part of the hand (cleft hand) to be discussed later.

It will be seen that this group of cases shows more or less involvement of most of the digits (second, third, fourth and fifth). Any single one of them, however, may be absent, although this is exceptional except in lobster-claw hand.

*Radial Hypoplasia.*—The typical expression is found in involvement of the thumb, as demonstrated in case 41 (fig. 10 *B*). This hand was normal except for a functionless rudimentary thumb. The phalanges were small but of fairly normal outline; the metacarpal was represented by a rudiment only. The appendage was flail-like and apparently lacked muscular connection. The patient had no control over it. This then is a typical hypoplasia of a pure radial element.

More or less involvement of the radial fingers may be present, as illustrated in case 25 (fig. 10 *A*). This patient had a bilateral lesion, hypoplasia with syndactylism. The right hand showed a loss of the distal phalanx of the thumb with a rudiment of the proximal phalanx. The index finger presented a fairly normal proximal phalanx with the distal phalanges absent, the middle finger a normal



Fig. 11.—Ulnar and radial hypoplasia in case 26.

proximal phalanx, rudiment of the second and absence of the third, all held together in syndactylism. The ring and little fingers were normal. The left hand presented a similar thumb and index finger. The middle finger was similar except that there was a symphalangism of the proximal phalanx with the second phalangeal rudiment. The ring finger was similar to the middle finger. The four digits were bound together in syndactylism. The little finger was normal. This patient was operated on, and the fingers separated.

*Bilateral Hypoplasia, Medial Parts Less Involved.*—CASE 26.—The child in this case presented hypoplasia of both ulnar and radial elements, the middle finger being the least involved (fig. 11). The first and fifth metacarpals were short and had no phalanges attached. The second, third and fourth metacarpals were normal, the second and fourth had no phalanges attached, but the third had a fairly well developed proximal phalanx with a rudiment of the second. All were bound

together in syndactylism; otherwise the hand was normal. A congenital scar is seen in the photograph on the ulnar side of the forearm.

CASE 34.—The patient in this case (fig. 12 *B*) presented only digits on the left hand. They were difficult to identify. It is probable that the thumb was represented by the radial rudiment, one digit was probably the index finger, the other probably the third. This is suggested because there was a cleft between the two digits extending down into the palm, a picture similar to that seen in cleft hand with an absence of the middle metacarpal and finger. No carpal bones were seen, although they may not have as yet ossified. The wide separation of the ulna and radius from the metacarpal suggested that some might be present. Some centers of ossification were seen in the normal right carpus. Neither the metacarpals nor phalanges of the two digits present were normal, but the digits showed fair function. All other metacarpals and phalanges were lost. This patient showed also a right club foot, short hypoplastic femur, no little toe, no fibula, only four tarsal bones, two metatarsal and four toes. The right hand was normal.

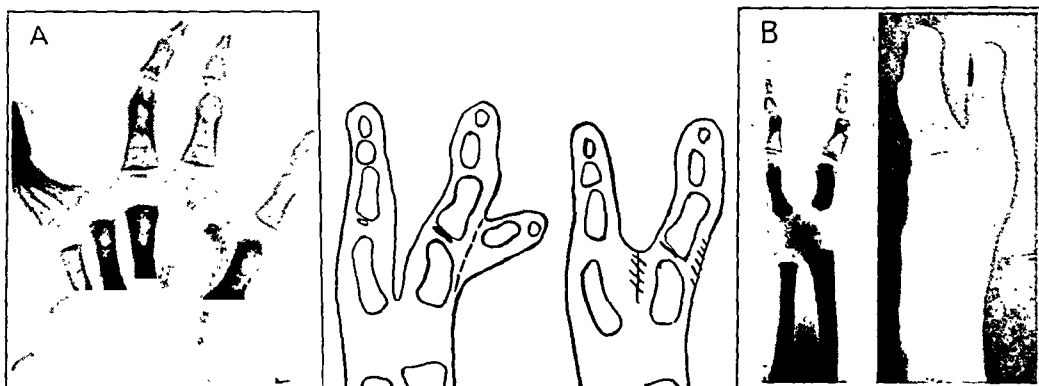


Fig. 12.—*A*, ulnar aplasia in case 14. *B*, ulnar and radial aplasia in case 34. Sketches of the preoperative and postoperative condition and a photograph and roentgenogram of the hand after operation are shown for case 34. (See schematic drawing, figs. 8 and 29.)

The thumb rudiment was removed, and the cleft sutured out to the end of the metacarpals after the manner to be described in the discussion on the treatment of cleft hands. The function following this procedure was satisfactory.

*Hypoplasia of Medial Elements (Lobster-Claw or Crab-Claw Hand, Perodactylus, Peromanus, Peropus, Perochirus).*—By the term “medial elements,” reference is made to the medial part of the hand in contradistinction to the lateral. The simpler and classic type, that of aplasia of the middle finger with part of its metacarpal has received undue attention owing to its striking pathologic picture, and some would reserve the term lobster-claw hand to this particular lesion. Even a cursory examination, however, discloses that it is but one phase of medial hypoplasia. Some authors have attempted to give descriptive names to the varying degrees of medial hypoplasia, but this is unjustified since



the variations are of degree and not kind. Every degree may be found from simple loss of the middle finger to complete loss of all medial elements with rudimentary elements of the first and fifth digits only remaining. Others have attempted subclassifications based on the position of the rudimentary metacarpals or phalanges present. This also is unnecessarily confusing since the varying position of these bones with the associated syndactylism is simply an expression of varying degrees of the associated disorientation. We will go much farther in our understanding of these cases if we disregard the unnecessary and unwise nomenclature and begin our study with the full understanding that the various types are but the expression of a greater or less degree of hypoplasia with associated disorientation.

**Etiology:** While we are convinced that the process is the result of local destruction of tissue having, in common with the hypoplasias already discussed, its origin in the germ plasm, yet because of its striking similarity to a picture that would appear if due to a nonunion of embryologic elements or to a reversion to the types of certain mammalian feet, these possibilities should be considered. This is particularly true if we were to confine our attention to the classic simple type of loss of the middle finger as some authors have done. The argument for reversion to ancestral type is based on the frequency with which a hereditary history is obtained, on the footprint of the *Thinopus antiquus* and the split foot of the lizards and salamanders.

Haim said that in 27 of 67 cases the history showed a hereditary tendency. Meyer reported a family of 20 in four generations, with 13 persons affected showing 13 split hands and 26 split feet. Lewis and Embleton found 180 individual cases, including some radial types of ectrodactylism, with a hereditary history in all but 13. In a family with 51 persons in four generations, 35 were affected. They believe, however, that it is not governed by mendelian laws and that swamping of transmitted sports will eventually take place. In reply to this, one has only to draw attention to similar histories of hereditary tendency obtained in almost all cases of hypoplasia of various degrees and of other types of congenital deformities in which no ancestral type could by any stretch of imagination be found.

As to ancestral forms, the imprint of a foot of some ancient mammal was discovered in a slab of sandstone in the uppermost Devonian stratum (Chemung) in 1896 by Professor Beecher of Yale (fig. 13 *A*). This is the earliest record of a mammalian foot. It is interpreted by Professor Lull as "presenting two completely formed fingers, probably the first and second, the cleft between them extending deep into the sole of the foot. The phalangeal pads and a rounded, terminal, claw-like portion are well developed and there appears on the outer side of the digit II the rudiment of a third—and below this the possible anlage of digit IV." While I have not had an opportunity to study this footprint,

yet I am inclined to agree with Morton, who after an examination, believes that the assumption of its form is not proved and that the footprint may be incomplete, the imprint of the other toe having been broken off and that instead of being a four toed mammal it was really true to type and had five toes and was really not a split foot.

The assumption that the split hand is a reversion to type as expressed by the salamanders and lizards cannot be dismissed so lightly. Robe studied the developing Triton, Wiedersheim presented studies in the

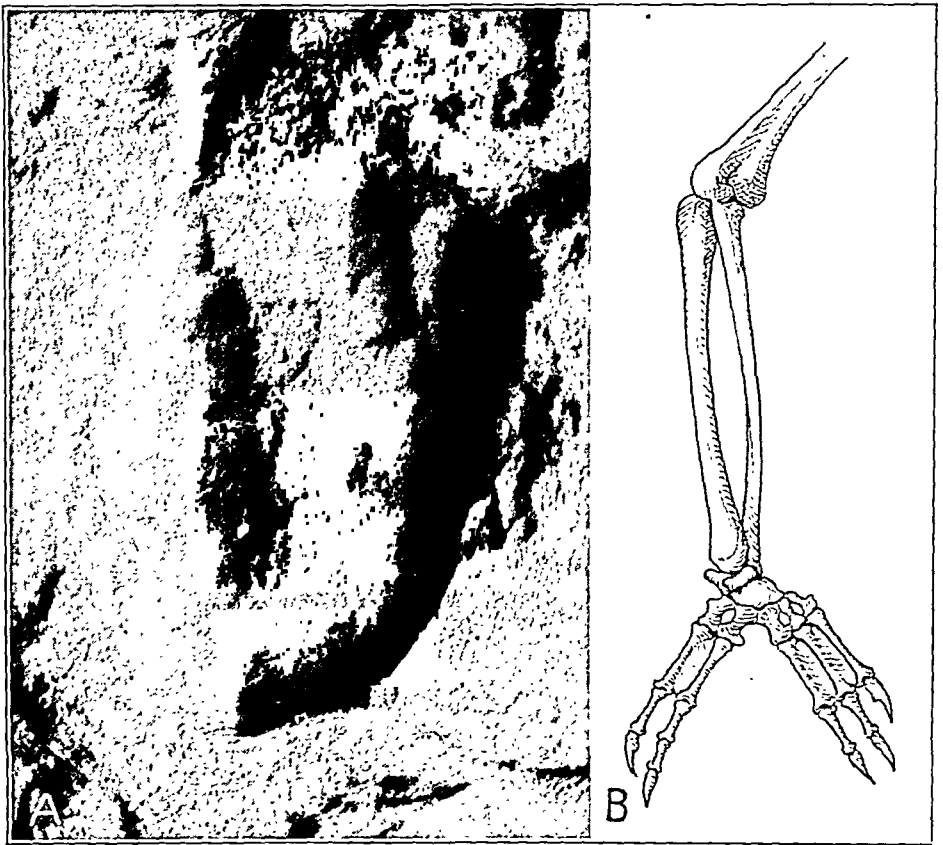


Fig. 13.—*A*, photograph of a cast of the footprint of the *Thinopus antiquus* (Marsh) (courtesy of Professor Lull). *B*, sketch of the bones as they lie in the foot of the *Chamaello jacksoni* Boulenger (courtesy of Field Museum).

comparative anatomy as shown in the *Ranodon sibericus*, and there are extant the chameleons giving proof of mammalian split feet. The drawing presented made from a specimen (*Chamaello jacksoni* Boulenger) in the Field Museum shows a foot split between the second and third digits extending almost to the carpal joint (fig. 13 *B*).

The embryologic origin of the hand has already been discussed, and did we not have weighty evidence to the contrary, we might be inclined to believe the split foot to be a reversion to this type. This evidence lies largely in the findings that the classic middle finger loss with the hand

cleft to the wrist is but the expression of a single phase of hypoplasia and every graduation of this from a loss of less tissue, e. g., part of the third digit, to complete loss of nearly all medial elements may be seen. To our mind the similarity of the classic type to the embryologic picture and the intriguing problem of its origin has induced an undue attention to this particular degree of hypoplasia with the collection of cases presenting this phase to the neglect of other and less interesting types. Moreover, the theory does not explain the disorientation of the surrounding tissue with its syndactylism and distortion of bony structure which is such a conspicuous part of the picture (fig 14).

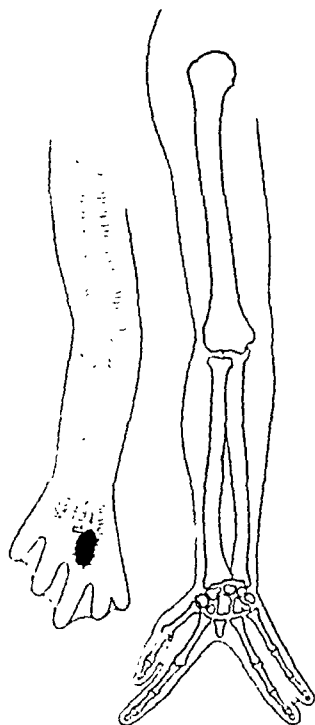


Fig. 14.—Schematic drawing illustrating genesis of lobster-claw hand following central necrosis and surrounding disorientation in the embryonal limb.

The clinical and pathologic picture in its varying degrees is well shown in the cases selected from our series.

*CASE 29.*—Bilateral medial hypoplasia; left syndactylism of first and second digits; polydactylism with double proximal phalanx of first digit; feet show bilateral medial hypoplasia, right, loss of phalanges of second digit; left partial phalangeal loss of second digit; syndactylism; bilateral stenosis of tear ducts; hypospadias; premature closure of fontanels; deficient growth of hair.

Baby H., aged 6 months, presented in the right hand the classic picture of lobster-claw with an absence of the phalanges of the third digit, the metacarpal, however, being present. The second and fourth digits were widely separated and pointed laterally rather than distalward. The thumb looked fairly normal and had good function. The index finger had two phalanges, no nail, was pointed, dis-

oriented with lateral curvature and flexion and had slight syndactylism with the thumb. The function was greatly impaired. A wide web extended over to the fourth and fifth digits. The fourth digit pointing ulnarward had a large base, partly bone and partly neuromatous tissue. Its function was good; all phalanges were present with the nail. The fifth digit was approximately normal (see fig. 15). The left hand was much more disoriented. It also presented the classic lobster-claw hand. Pathologically, the bones of the thumb were normal except that there was apparently a doubling of the first phalanx. The index finger was markedly distorted, bound in syndactylism with the thumb; the first phalanx articulated distalward with the supernumerary first phalanx of the thumb, and a distorted second



Fig. 15.—Median hypoplasia with loss of the middle finger and part of its metacarpal, bilateral, in a case of lobster-claw hand (case 29). The x-ray pictures were made before operation; the photographs, after operation.

phalanx was held in about 60 degrees radial abduction. The metacarpal of the third digit was present, and the first phalanx lay transversely, articulating distally with the metacarpal of the fourth digit and its disoriented first phalanx. The other phalanges were absent. The fourth digit was fairly normal except for the poorly developed first phalanx. The fifth digit was approximately normal.

*Operation.*—Due to the extensive disorientation, the operative procedure was divided into stages. First stage, right hand: An incision was made from the middle of the proximal phalanx of the ring finger on its radial side passing along the extended web to the middle of the proximal phalanx of the index finger on its

ulnar side. From here the incision encircled the proximal phalanx of the index finger near its base, the skin only being incised. The skin was now dissected from the dorsal and flexor surfaces for a sufficient distance proximalward to permit shifting of the entire index finger and its metacarpal ulnaward after adventitious bands were severed. The fascia and connective tissue was separated on the palmar surface from the metacarpal bone of the absent middle finger and three fourths of the metacarpal bone removed. A heavy catgut suture passing through the periarticular fascia then brought the distal ends of the metacarpal bones of the index and ring fingers together. A second heavy catgut suture passed in a similar manner brought the proximal ends of the proximal phalanges in close apposition. Some excess connective tissue was removed, and the edge of the skin incision sutured, dorsal surface to flexor surface. It will be noted, however, that the index finger now occupies a position more ulnarward than previously, and here, of course, the flexor skin of the palm was sutured to the flexor skin of the finger, dorsal surface to dorsal surface. This shifting of the finger, but not the skin, also provided a more extensive web between the index finger and the thumb (see fig. 24). The suturing was reinforced during the dressing by adhesive tape around the palm and around the index and ring fingers. By this means a normal palm was restored, and the fingers were held in apposition all pointing distalward as in the normal hand. First stage, left hand: An incision was made along the web transversely from the ulnar side of the index finger to the radial side of the ring finger. The palmar fascia and connective tissue were dissected free from the transversely lying first phalanx of the middle finger and its metacarpal. The phalanx and the distal three fourths of the metacarpal bone were removed. The flexor tendons going to the index finger and thumb could be seen and traction caused flexion of the thumb, but not of the index finger. A second incision was then made on the dorsum of the hand to the radial side of the first phalanx of the index finger extending one-half inch (1.27 cm.) on the dorsum of the hand and a less distance on the flexor surface. The supernumerary proximal phalanx of the thumb was removed. The connective tissue holding the distorted index finger was excised, the index finger brought over to the ring finger and the two sutured together in a manner similar to that described for the right hand. The transverse web skin incision was sutured, flexor surface to flexor surface, dorsal to dorsal, and not flexor to dorsal as it was originally lying. This eradicated the cleft and restored a normal palm.

The second incision was closed, the flexor surface being sutured to the dorsal surface so as to make a slightly improved though still unsatisfactory thumb-index web. The hand was dressed, and adhesive tape was placed circularly about the palm and the index and ring fingers, so as to maintain the normal contour of the palm and to hold the fingers in their proper relation. The thumb was dressed, abducted from the index finger. It was thought wise to defer a plastic operation to restore a normal thumb-index web until a later period.

Second stage, right hand: Two months after the first stage the wounds were well healed. Since the distorted index finger did not move freely, an incision was made along the flexor part of the scar between the index and middle fingers, and the scar and connective tissue was removed from about the tendon of the index finger and along its flexor surface to permit more free extension of the finger. Second stage, left hand: Since there had been some separation of the index and middle fingers, an incision was made along part of the line of the old scar, and new sutures were inserted to hold the proximal phalanges of these fingers in better apposition. The flexor tendon of the index finger that had been found to be inactive at the first operation was dissected free with the hope that some function of this

finger could be restored. The attempt was not satisfactory in that fibrous ankylosis of the interphalangeal joints was found. The finger, however, was straightened as much as the disorientation of the bones of the phalanges would permit. A second incision was made transverse to the web of the thumb and index finger. The scar tissue and the bands of connective tissue of congenital origin holding the thumb in apposition with the index finger were removed. A full thickness free skin graft was then taken from the abdomen and sutured in position to make a new web with wide separation of the thumb and index finger. Sponge pressure was applied to the skin graft. All wounds healed kindly and the skin grew in place.

The result of these various operations was that supernumerary bones were removed, the ring and index fingers brought into apposition, the palm was restored and the fingers placed in normal relation to the palm. The thumb was separated from the hand so as to act in its normal relation to the palm and fingers. The appearance of the hand, fingers and thumb was excellent and the function satisfactory. Unfortunately, the disoriented bones and tendon of the index finger of the left hand impaired the function in this digit. The index finger of the right hand was also disoriented, but had a moderate function. All other digits functioned satisfactorily.

The after-treatment consisted of splinting to maintain the index finger in its proper position during growth and physical therapy to restore and improve function in the thumb and other fingers. An examination three years after the operations disclosed an excellent function which it is believed will improve with the development and use of the hands. The appearance is excellent (see fig. 15).

CASE 31.—*Bilateral medial hypoplasia, syndactylism.*

The patient, a baby, was referred through the courtesy of Dr. Teitelbaum. The right hand was difficult to orientate. There was either an absence of the index finger or its fusion with the thumb, probably the former. The metacarpal of the index finger showed beginning reduplication. There was a wide separation of the thumb from what was apparently a disoriented middle finger. The phalanges were large, and it might be there was fusion of the middle and ring proximal phalanges since the ring finger appeared to be absent although its metacarpal was intact. The little finger was apparently normal.

The left hand showed an intact little finger. All metacarpals were normal. There was complete syndactylism of the middle and ring fingers with distal fusion of the distal phalanges. The thumb and index finger showed syndactylism throughout their length, the bones being separate. The hand presented a wide cleft between the index and middle fingers due to the radial syndactylized group pointing radialward and the ulnar group, ulnarward (fig. 16).

At the time the patient was presented it was deemed wise to defer operative procedures. A poor prognosis was given as to possible results from treatment of the right hand; in the left, however, almost complete functional and cosmetic result should be obtained by plastic procedures.

CASE 30.—*Bilateral medial hypoplasia, syndactylism.*

The patient when first operated on was 2 months of age. At this time the hypoplastic bones were removed and the median cleft repaired. Eighteen months later the syndactylism was treated.

On examination, the right hand presented a loss of the middle finger with a median cleft extending halfway up the palm and moderate syndactylism between the little and ring fingers. Roentgen examination disclosed an absence of the middle finger, a hypoplastic middle metacarpal and apparently overgrowth of the index metacarpal. The left hand presented a similar cleft with absence of the middle finger, complete syndactylism between the thumb and a greatly distorted index finger and moderate syndactylism between the little and ring fingers. Roentgen examination disclosed normal bones of the little and ring fingers. The middle finger was absent, its metacarpal present but bound with the syndactylized radial elements. There was an overgrowth of the proximal phalanx of the index finger due either to a complete fusion of this with the proximal phalanx of the middle finger or to a hypertrophy of this element. The distal phalanx of the index finger was smaller than normal. In both hands the ulnar group was directed ulnarward and the radial group, radialward instead of projecting distalward as in the normal state (fig. 17).

*Operation.*—First stage, right hand: A transverse incision was made along the cleft extending from the ulnar side of the index finger to the radial side of the



Fig. 16.—Second degree of median hypoplasia of the right and left hands in case 31 (courtesy of Dr. Teitelbaum).

ring finger. The dorsal and palmar flaps were dissected up, and the rudiment of the middle metacarpal removed down to its proximal end. The metacarpal bones of the ring and index fingers were then approximated and held in position by catgut sutures. The connective tissue and skin were then sutured, flexor surface to flexor surface, dorsal to dorsal, and not dorsal to flexor as they had originally lain when incised. The palm and the ring and index fingers were further supported in their new position by circular bands of adhesive tape applied over the dressings. Later experience has shown that we should have sutured the base of the proximal phalanges together to prevent lateral deviation of the digits. This was done at the second stage. First stage, left hand: The repair of the cleft and the removal of the rudimentary metacarpal were carried out in a manner similar to that on the right.

In the second stage of the operative procedures the syndactylisms were destroyed and webs made by lateral flaps from the adjacent fingers, the defects on the sides of the digits being covered by Thiersch grafts; while the result was excellent, later experience has convinced us that in such major syndactylisms as presented in the

left thumb-index digits a bold incision and dissection followed by a full thickness free skin graft is in general followed by more certain good results.

Second stage, right hand: To correct the moderate syndactylism between the fourth and fifth digits, two flaps of skin were raised from the sides of the little and ring fingers respectively, with the pedicles on the dorsum and the two flaps sutured to the flexor surface, making a new web at the proper site. The denuded lateral surfaces of the fingers were covered by Thiersch grafts and pressure sponges applied.

Second stage, left hand: The syndactylism between the fourth and fifth digits was corrected by a similar procedure to that used in the right hand. The syndactylism between the thumb and index finger was corrected by raising a U-shaped flap dissected from the web and the adjacent sides of the digits, the base being on the dorsum. The congenitally contracting connective tissue was removed, the thumb well abducted and the raised flap brought between the digits and sutured on

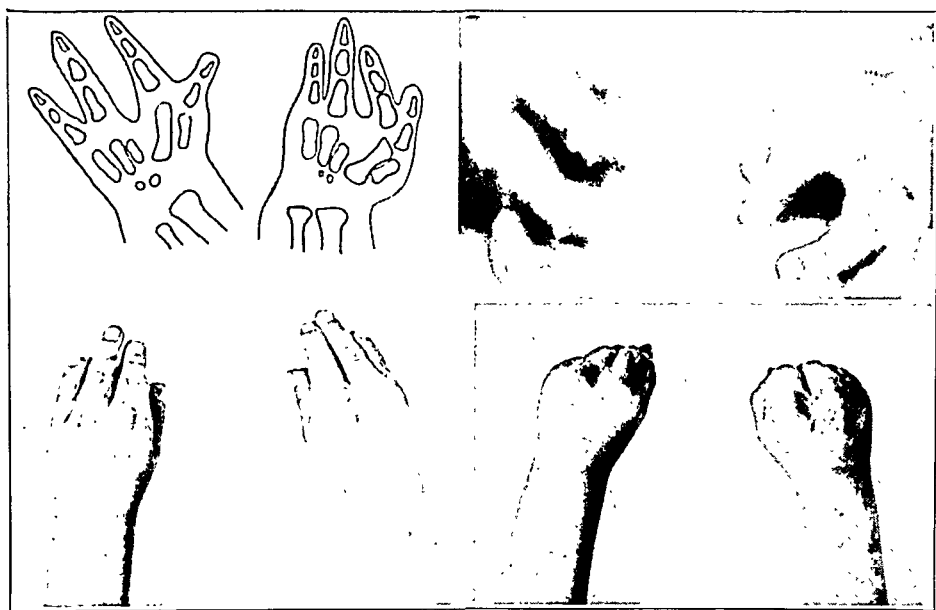


Fig. 17.—Median hypoplasia in case 30. The upper photographs were made before operation; the lower photographs show the result at the end of five years after operation.

the flexor surface. The denuded area left on the digits was covered by Thiersch grafts and pressure sponges applied.

All wounds healed well, and the function of all fingers was excellent. The result after five years may be seen by the accompanying photographs (see fig. 17). At that time the father wrote, "The child does not seem to be handicapped in any manner. He can use a sewing needle, scissors, tools and his handwriting is above normal for a child of four years."

CASE 32.—*Right unilateral medial hypoplasia, syndactylism and mongolianism.*

Boy B., aged 13, except for the mongolianism, presented no defects other than median hypoplasia and syndactylism of the right hand. The hand had a median cleft extending up to the carpal bones with a complete absence of the middle finger and its metacarpal (fig. 18). There was a moderate syndactylism between the little and ring fingers, both fingers being well formed. The thumb and index finger



were bound in complete syndactylism presenting the appearance of one large digit. The deformity was marked, and the function much impaired. The x-ray pictures (fig. 18) disclosed a complete absence of the middle finger and its metacarpal, normal bones in the ring finger, the two distal phalanges of the little finger present but hypoplastic and the articulations distorted. In the thumb and index finger the metacarpal bones and the proximal phalanx of the index finger were normal, the distal half of the first phalanx and the distal phalanx of the thumb were absent and there were rudiments only of the second and third phalanges of the index



Fig. 18.—Third degree of median hypoplasia in case 32.

finger. The carpal bones were apparently normal. The thumb and index finger were widely separated from the ring and little fingers. At operation the tendons of the index finger and the thumb were found to be in partial fusion; the function of the flexor tendon of the thumb was much impaired, and the tendon going to the index finger was abnormally short.

*Operation.*—The operative treatment was divided into two stages. At the first stage the thumb and index finger were separated throughout their length, care being exercised to preserve the blood and nerve supply. The partially fused tendons were separated. A full thickness free skin graft from the abdomen was applied to the web and to the denuded lateral surfaces of the two digits extending to the ends

of the digits. A transverse incision was made from the ulnar side of the first phalanx of the ring finger through the cleft to the radial side of the first phalanx of the index finger. Some skin and connective tissue was excised, and the metacarpal bones of the two fingers were sutured together. The proximal ends of the first phalanges were then sutured side to side, and the skin edges were sutured flexor surface to flexor and dorsal to dorsal. Pressure sponges were applied to the large skin graft, and the hand was dressed. The graft healed in place well except for about one-half inch covering the end of the rudimentary index finger. The appearance of the hand was excellent when the patient left the hospital at the end of three weeks, but about a week later there was some separation of the distal ends of the sutured metacarpal bones followed by curvature of the hypoplastic end of the index finger. The thumb tendon failed to give completely satisfactory function, although it was believed that this would improve.

In retrospect, it is believed that we would have been wiser had we transferred the shortened index flexor tendon to the thumb and thus given better function to the newly made thumb. This would have sacrificed function to the distal phalanges of the index finger, but this function in the hypoplastic phalanges was of little importance at best. Moreover the short tendon to the index finger being under tension had tended to produce a separation of the metacarpal heads.

At the second stage the syndactylism between the first phalanges of the little and ring fingers was destroyed by a longitudinal incision of the web, care being taken not to destroy the nerve and blood supply, and a free full thickness skin graft from the abdomen was inserted to cover the defect, after our usual technic. Through an incision along the old scar between the index and middle fingers the heads of the metacarpals and the bases of the proximal phalanges of the index and middle fingers were approximated with sutures, and the hypoplastic, distorted, distal phalanges of the index finger were removed. At the dressing a circular adhesive tape was applied to help hold the metacarpal bones in apposition until healing was complete.

The result of these various operative procedures was that the patient had a much more presentable hand with fair function, although it is believed that a transference of the flexor index tendon to replace that of the thumb would improve the thumb action.

CASE 28.—*Medial hypoplasia of left hand; right normal.*

Baby W., who was 13 months of age when she came to the clinic, presented no congenital deformities except in the left hand, which showed absence of the middle and ring fingers with marked contracture of the index and little fingers, which were curved toward each other so that the tips touched. Roentgen examination disclosed a complete absence of the ring finger and a remnant only of the proximal phalanx of the middle finger, with both metacarpals present but distorted. The thumb was normal; the index and little fingers showed all bones present but distorted. Small knobs of tissue were present, representing the middle and ring fingers.

*Operation.*—An incision was made extending from the middle of the side of the index finger across the web to the side of the little finger. That part crossing the web was of an exaggerated S shape. The two convex parts extended well down on the dorsal and palmar surfaces respectively, so as to make two pedicled flaps one with its base on the dorsum and the other on the palm, the one on the radial side being larger. The remnant of the first phalanx of the middle finger and the head of its metacarpal were removed. The contracting congenital bands were then dissected away from the index and little fingers so that they could be straightened. The radial flap was now sutured to the side of the index finger to cover its exten-

sively denuded surface, and the other flap covered the less denuded surface of the little finger and made a web between the two fingers. Pressure sponges were applied, and the flaps healed in position. The result gave excellent function, although the absence of the two fingers permitted some lateral deviation of the fingers to recur.

CASE 24.—*Left medial hypoplasia and syndactylism; clinodactylism.*

Baby H., aged 4 years, was born with syndactylism of the four fingers, clinodactylism with hypoplasia of the middle phalanx of the little finger and hypoplasia of the index, middle and ring fingers. The thumb and all metacarpal bones were present. There was a rudiment consisting of about one half of the proximal phalanx of the index finger, a similar amount of the first phalanx and a rudiment of the middle phalanx of the middle finger, and a fairly well developed proximal phalanx and a small rudiment of the second phalanx of the ring finger (fig. 19).

At a previous operation elsewhere the little finger had been separated from the ring finger. At our clinic the three middle fingers were separated by longitudinal incisions, and free full thickness skin grafts were applied after the manner described in the section dealing with syndactylism. The functional and cosmetic results were satisfactory.

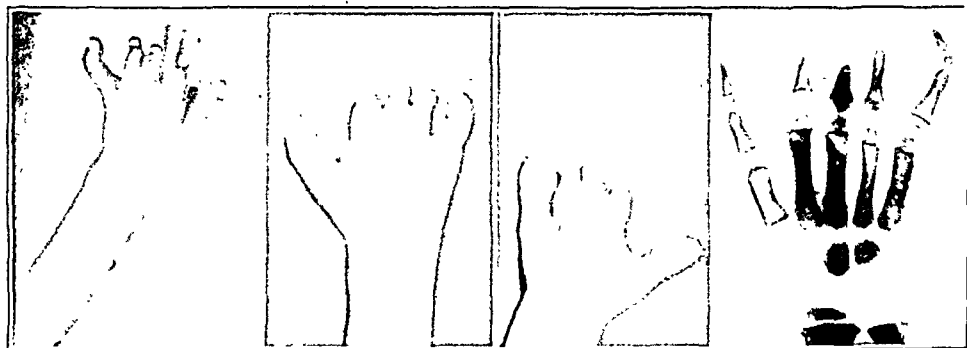


Fig. 19.—Median hypoplasia clinodactylism in case 24.

CASE 35.—*Medial hypoplasia, left hand.*

This patient, presented through the courtesy of Dr. Goldstine, had a complete cleft of the left hand extending to the wrist with two digits present, apparently the first and fifth. The function was excellent. The bones of the thumb as well as the metacarpal showed hypertrophy. The metacarpal of the little finger was intact, but there were only two phalanges, the distal appearing as a normal phalanx. It was impossible to say whether the first and second phalanges were fused or that one had been lost. Two small rudiments of medial metacarpals were present, believed to be from the third and fourth metacarpals (fig. 20 A).

The function of the hand was so good that operative treatment was not advised.

CASE 36.—*Medial hypoplasia, left hand; absence of pectoralis major, left; hypoplasia of pectoralis minor, left; symphalangism.*

The patient, aged 24 years, presented a history showing hereditary tendency. She had excellent use of the deformed hand, and grasped well between the two digits (fig. 20 B).

The hand consisted of two digits, one a radial (thumb) and one an ulnar (little finger). The radial digit carried no nail, and there was apparently a loss of the distal phalanx. The metacarpophalangeal joint showed excellent function, but the carpometacarpal joint was lax and the metacarpal slipped radially and dorsally on use. The carpometacarpal joint of the little finger was intact and function was

excellent. The phalanges were fused at the joints, and the head of the fused finger lay anterior to the head of its metacarpal although flexion was present and a gliding motion in the transverse and vertical axis was permitted. Rudiments of the metacarpals of the second, third and fourth digits were present where small nodules the size of a pea were seen.

Owing to the excellent function of the hand, no operative procedures were advised.

The extreme type of medial hypoplasia is reported by Seroiczkowski.<sup>9</sup> The patient presented a bilateral median hypoplasia with one carpal cartilage and two small rudiments, representing a single bone of the thumb and little finger, respectively. The hands were similar, and both feet presented an almost identical picture. A more extreme similar lesion with loss of the radial hand and ulnar hypoplasia is reported by

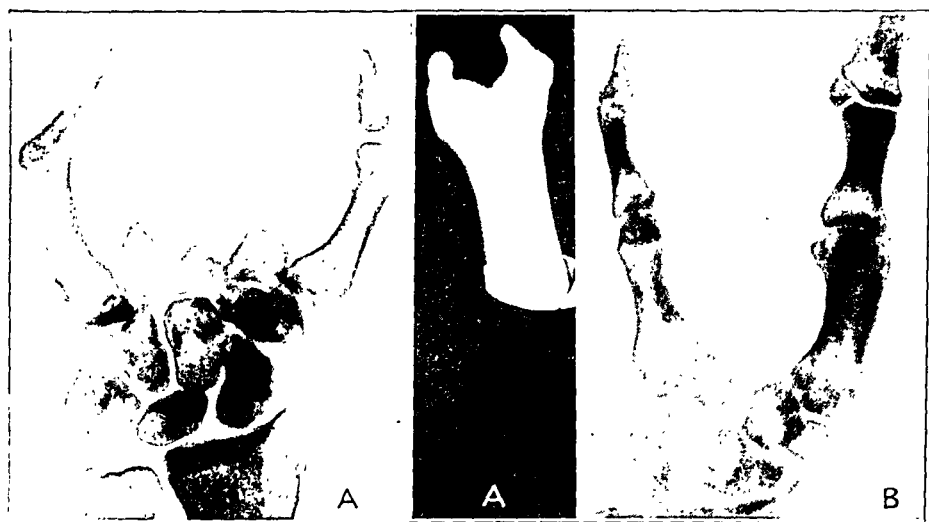


Fig. 20.—Roentgenogram and photograph (A, A) showing median hypoplasia, fourth degree, in case 36. (Courtesy of Dr. Goldstein.) Roentgenogram (B) showing atypical hypoplasia in case 35. There is no certainty as to absent digits.

Jaroschy in which the radius and ulna of the left forearm are widely separated at the distal ends (fig. 21).

These varying clinical pictures are seen to present varying degrees of medial hypoplasia with the remaining ulnar and radial elements pointing laterally instead of distalward. At times the middle finger only or the middle finger with its metacarpal is involved. In others, the middle and ring fingers, or the middle, ring and index fingers, or the middle, ring and little fingers with a lesser degree of hypoplasia of the thumb and index fingers are found involved with varying degrees of loss of the metacarpal and carpal bones. We often find hypoplasia of

9. Seroiczkowski, A.: Symmetrical Malformation (Cleft) of Hands and Feet, *Ztschr. f. d. ges. Anat.* **89**:145, 1929.

a digit and disorientation of its remaining elements. This disorientation frequently is expressed by a transversely lying proximal phalanx or metacarpal. These cross-lying bones seem to bridge the defect, and they may articulate with adjacent articulations, e. g., a transversely lying metacarpal with the articulation of an adjacent metacarpal and its phalanx, or a cross-lying phalanx with adjacent and interphalangeal articulation. To our mind, unjustifiably, Lewis and Embleton dignify these variations with descriptions as distinct types. We believe them to be but an expression of varying degrees of disorientation and not clinical entities. The adjacent bones may show hypertrophy, and the question arises whether this is a simple hypertrophy or an enlargement due to fusion of two elements. The lateral disorientation is con-

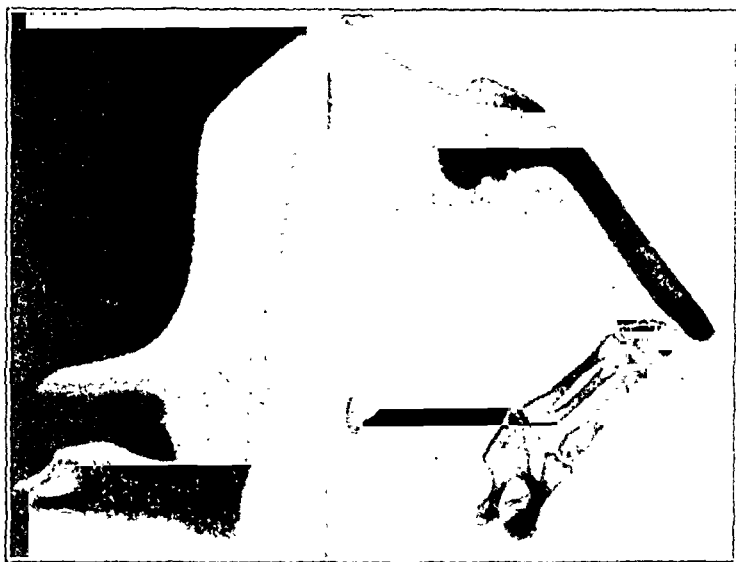


Fig. 21.—Excessive separation of the ulnar and radial elements with loss of the medial and radial digits, metacarpals and carpals. (From Jaroschy: *Arch. f. orthop.* 25:482, 1927.)

spicuously present and is most frequently expressed by moderate hypoplasia of various bone or muscle elements and syndactylism, especially on the ulnar side. Kummel reported that in 17 patients there were 7 hands with radial syndactylism alone, 21 with ulnar and 3 with both ulnar and radial. In our observations bilateral syndactylism of the involved hand is more commonly present. Polydactylism is less often present. At times we find a rudimentary extra digit at the end of a phalanx.

Associated lesions are not uncommon, e. g., deformity of the lower end of the radius, absence of the pectoralis major or minor and various other lesions. Very frequently we find involvement of the feet and a similar lesion. In 59 persons, Perthes found one hand involved in 11 cases,

both hands in 5, both feet in 9, both feet and one hand in 4, both hands and both feet in 30. In 48 of the 59 patients more than one extremity was involved.

Spurious split hand may be produced by lack of differentiation of metacarpal bones. This is illustrated by the patient presented by Bircher<sup>10</sup> (fig. 22).

Treatment: Much can be done for the simpler types of median hypoplasia. The treatment consists of surgical restoration followed by splinting and physical therapy. The purpose of the surgical treatment is the restoration of the fingers and tendons to the position of function and cosmetic effect. Function depends on the position of the fingers



Fig. 22.—Spurious lobster-claw hand. (From Bircher: *Beitr. z. klin. Chir.* **121**:187, 1918.)

and the degree of disorientation of the muscles, nerves, tendons and joints remaining. The fingers can be placed in a relatively normal position, the function of the joints may be improved and tendons may be transplanted, but we know of little that can be done for impaired function of the intrinsic muscles and nerves except use and physical therapy. Fortunately, nature in time does much for these, and the hand, while not functioning after the usual pattern, still develops a function of its own that serves almost all purposes. This is due to the development of the intrinsic muscles working in their own peculiar way and to the fact that the fingers are moved by the forearm muscles which are little involved.

10. Bircher, E.: Die Gabelhand, zugleich ein Beitrag zur Theorie der Miss-Bildungen, *Beitr. z. klin. Chir.* **111**:187, 1918.

Operative Treatment: This may be divided under four heads: (1) restoration of the proper position of the fingers, (2) treatment of the associated tendons, (3) treatment of the associated joints and (4) treatment of the syndactylism and polydactylism.

These procedures are generally so extensive as to demand that the operation be divided into two and sometimes three stages. The work done in these stages naturally varies with the conditions. Generally, at the first stage the fingers are restored to their correct position and such other work as may be advisable is carried out, and at the second the syndactylism is treated.

When the cleft extends into the palm the primary incision generally lies transversely along the web, reaching halfway up on the proximal phalanges of the separated intact fingers. This simple incision is especially advised when there is more or less cleft of the palm. When the palm is intact it may be advisable to carry the transverse incision of the web around the base of the proximal phalanx of the index finger. In the first instance the purpose is to permit restoration of the palm when the fingers are approximated. In the second the purpose is to permit transference of the index finger to lie adjacent to the ring finger. This avoids sacrifice of skin which is used to make a web between the thumb and index finger. Special conditions will demand variations of these incisions.

In the first type of operation the incision of the skin having been made, it is dissected free from the underlying tissue and all transverse-lying or disoriented bones removed, care being used not to destroy nerve and vascular tissue (fig. 23). A deep dissection is then made of the metacarpal of the affected finger, and this is removed down to its base. This leaves a defect and permits us to approximate the lateral-lying metacarpals. Care should be exercised to see that the sutures bringing these together are passed through firm tissue since there is a tendency for the bones to separate. We, therefore, use heavy chromic catgut and pass two or three sutures, attempting to bring the heads of the metacarpals in close apposition. The fingers also have a tendency to lateral deviation and the joint surfaces have grown in the distorted position so that it is necessary to pass one or two sutures through the tissue at the proximal end of the proximal phalanges to hold them in close apposition. The skin and subcutaneous tissue are now sutured. The subcutaneous tissue on the palm is so sutured as to leave an elevation rather than a longitudinal depression in the palm. The skin is sutured, flexor surface to flexor surface and dorsal to dorsal, not flexor to dorsal as originally found. In the dressing, circular strips of adhesive plaster encircle the dressed palm and fingers so as to support the suture of the bones. This should be maintained for three weeks at least since there is a marked tendency for them to separate.

If the palm is intact and there is not a marked syndactylism of the index finger and thumb, the radial end of the transverse incision of the web passes around the base of the proximal phalanx of the index finger. This permits us to dissect away the skin without impairing the blood supply, the intervening bones having been removed as previously

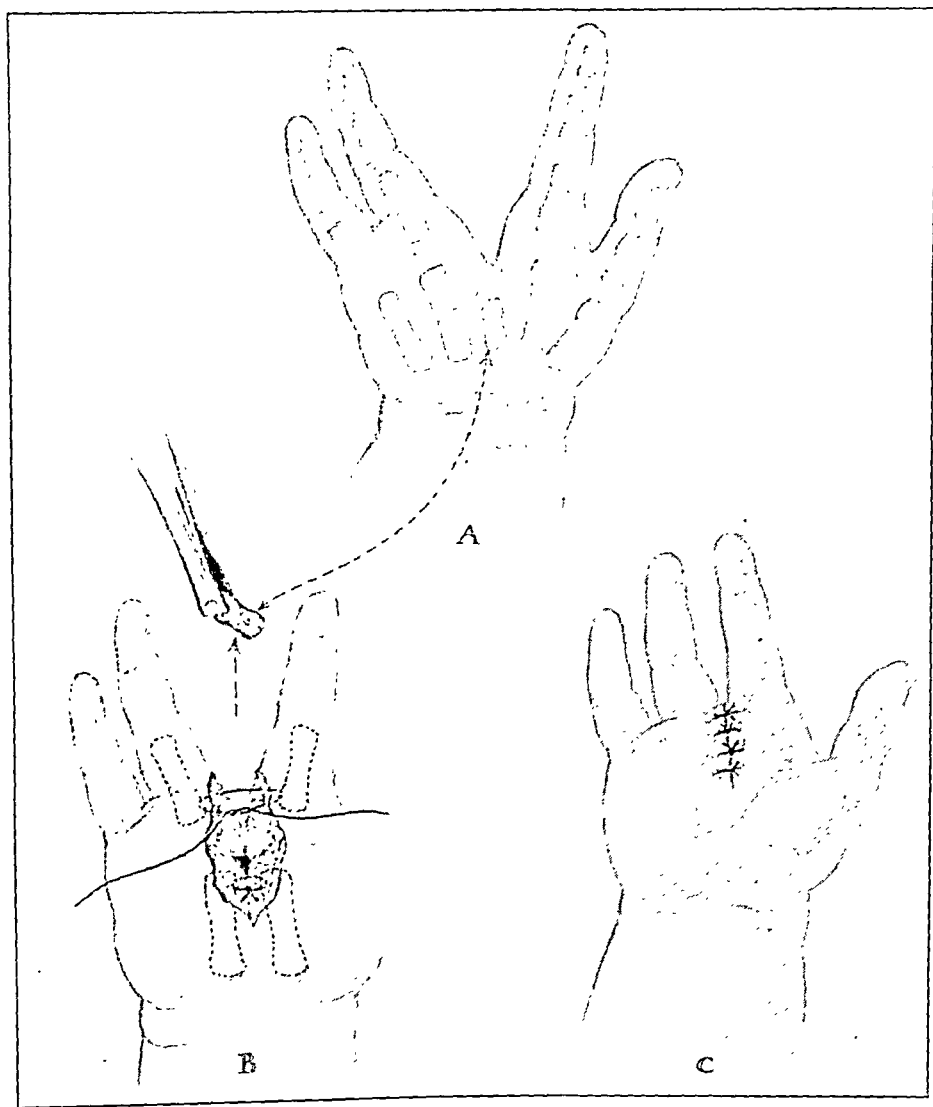


Fig. 23.—Technic of union of the ulnar and radial elements in lobster-claw hand.

described; to transfer the dissected index finger over to its prepared bed beside the ring finger, and to use the skin thus left on the radial side of the index finger for a web between the index finger and the thumb (see fig. 24 and case 29). The dressing and associated procedures are as previously described. This operation has not been used in cases in which there is extensive syndactylism between the index finger and the thumb since it is feared that the extensive dissection



necessary followed by skin grafting to cover the defect might impair the blood supply of the index finger, especially since sponge pressure is used in the after-dressing of the free skin grafts. Manifestly, varying conditions may demand modifications of these two typical procedures that have been used most frequently.

Generally, no operative treatment on the tendons is necessary since if they are disoriented the associated finger is also useless. At times, however, a tendon may be found in the same synovial sheath with an adjoining tendon, or it may be fused or absent. If in the synovial

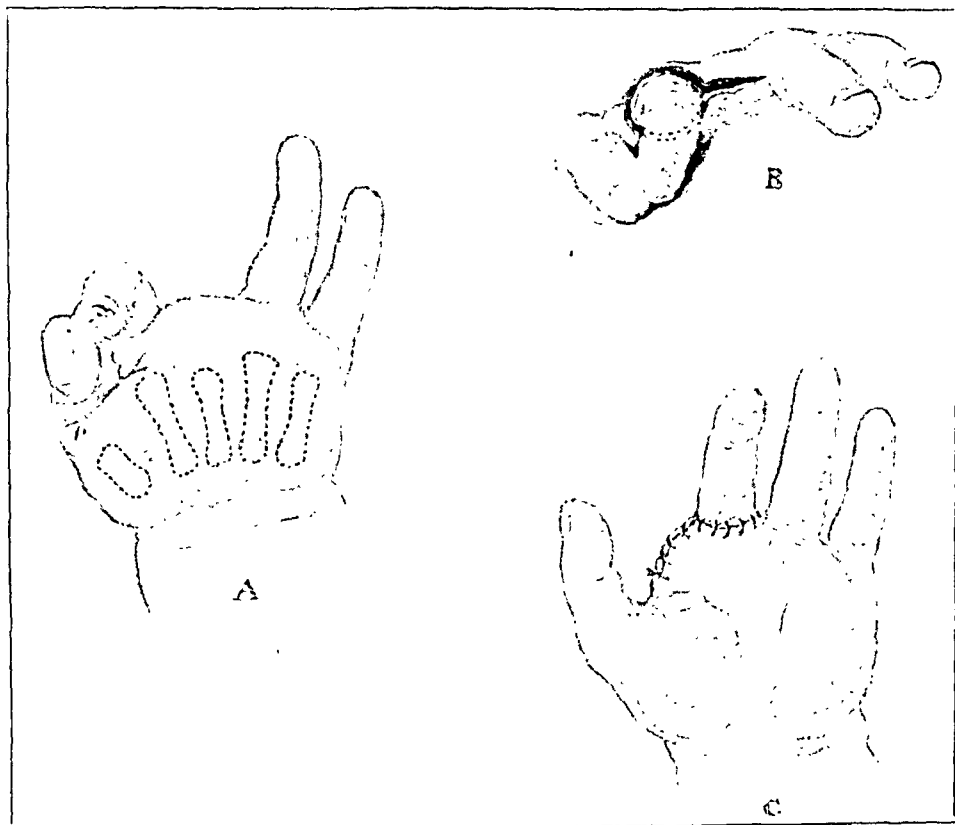


Fig. 24.—Technic of sliding operation for the index finger in certain types of lobster-claw hand.

sheath of an adjoining tendon, it may be removed from the common sheath and placed with its proper finger, or a good tendon of a distorted finger may be transferred to take the place of a poor tendon. This latter step is most frequently demanded if we wish to restore function to the thumb, which is very important. The index tendon may then be used if the index finger is hypoplastic, but if this finger is functioning, a tendon may be transferred later from the foot.

At times symphalangism may be present, and it may seem advisable to treat the condition at the time of the primary operation or later, especially if the bones are distorted. More frequently, however, it is neces-

sary to repair a joint because of a distorted relation of the joint surfaces or because a transversely lying metacarpal or phalanx that had joined with the bones of the adjacent finger, making a common articulation, had been removed. At other times it will be found advisable to remove hypoplastic bones from fingers which we are preserving either for cosmetic or functional purposes. This applies to the distal phalanges most commonly.

The repair of the joints is not infrequently associated with the removal of congenital contracting bands which hold the distal phalanges in a distorted position, e. g., clinodactylism.

The treatment for syndactylism is the same as that discussed in the section dealing with that subject. Ordinarily, since the syndactylism involves the thumb and index finger and the little and ring fingers, the treatment is carried out in two stages, since we fear that an operation involving both sides of the index and ring fingers at the same time might impair their vitality either by the necessary dissection or the subsequent sponge pressure used on the skin graft.

When the hand is restored to as nearly normal relation as possible, we may find it advisable to institute physical therapy to stretch tendons, destroy contractions and develop muscles. We also have at times made tension splints to supplement these procedures, the splints being designed on the principles described elsewhere in the discussion on that subject. Again we have made a detachable aluminum finger splint designed to hold a distorted finger in position so that newly made joints or distorted bones may grow in a proper relation. These are made after the type of the Lewin splint used in the treatment for ruptured extensor tendons of the distal phalanges.

The results obtained in our experience are often surprisingly good, especially after a few years of use of the restored hand. Cosmetically, the absence of the middle finger is hardly noticed; functionally, the hand may be almost perfect (see case 30, fig. 17).

*(To be Concluded)*

# MONARTICULAR ARTHRITIS SIMULATING TUBERCULOSIS

A CLINICAL AND PATHOLOGIC STUDY OF  
TWENTY-FOUR CASES

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The common occurrence of a type of monarticular arthritis that frequently simulates tuberculosis very closely is indicated by a study of a series of cases in which the patients were treated at the New York Orthopaedic Dispensary and Hospital and the results of which are presented in this paper. Few references to the condition appear in the literature. Friedrich<sup>1</sup> and Spitzzy<sup>2</sup> mentioned that monarticular arthritis may be mistaken for tuberculosis and that the differential diagnosis is often difficult. A conviction, which has become more firmly established with added experience, that in many instances of chronic diseases of the joints a diagnosis cannot be made without exploratory operation, biopsy and tests on guinea-pigs<sup>3</sup> has led to the discovery of this group of cases, which presents a number of interesting features.

From March, 1924, to January, 1930, twenty-four patients with such cases were operated on in the New York Orthopaedic Hospital. In each case the chief purpose in operating was to establish a diagnosis. A careful tissue examination was made in all cases, and, with two exceptions, a guinea-pig test was done. The presence of tuberculosis was excluded in each instance. The joints involved were: the knee, in eighteen cases; the hip, in four; the elbow, in one, and the tarsus, in one. The ages of the patients at the time of operation varied from 19 months to 35 years, the average being 14½ years. Fourteen patients were females and ten males. After consideration of all the available data, including a careful history and physical examination, roentgenograms, blood counts and tuberculin tests, the diagnosis in the twenty-

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From the clinic of the New York Orthopaedic Dispensary and Hospital.

1. Friedrich, H.: *Unspezifische Gelenkentzündungen unter dem vollen klinischen Bild der Tuberkulose (Scheinbare Tuberkulosen, Pseudotuberkulosen)*, München. med. Wchnschr. **75**:1153 (July 6) 1928.

2. Spitzzy, H.: *Zur Diagnostik der Knochen und Gelenktuberkulose*, Med. Klin. **17**:1 (Jan. 6) 1921.

3. Smith, A. DeF.: *The Early Diagnosis of Joint Tuberculosis*, J. A. M. A. **83**:1569 (Nov. 15) 1924.

four cases before operation was: synovitis (probably tuberculous) in ten, tuberculosis (without qualification) in ten, chronic or subacute arthritis in two and internal derangement in two. It is thus seen that in the majority of cases the diagnosis was wrong, and that the condition with which it most frequently was confused was tuberculosis, in twenty of twenty-four cases. The duration of the symptoms, which varied from a few months to as many as ten years, with involvement of only one joint, was suggestive of tuberculosis. In one case, the presence of a chronic pulmonary infection, which at first was believed to be tuberculosis but which afterward was diagnosed as streptococcus infection, suggested that the process in the knee also was tuberculous. In two of the patients an injury to the knee, followed by swelling, limitation of motion and tenderness over the medial meniscus, prompted the diagnosis of injury to that structure.

The physical examination in practically all of the cases revealed the classic signs of tuberculosis of the joints, namely, swelling with little tenderness or heat, limitation of motion from muscle spasm and atrophy of the adjacent muscles. There can be no question that these signs are just as common in any other chronic inflammation of a joint as in tuberculosis, and that they can be given no great weight in making a diagnosis. It was interesting to find that in nine of these patients, all of them children with involvement of the knee joint, the affected leg was from  $\frac{1}{4}$  to 1 inch (0.64 to 2.5 cm.) longer than the normal one. This had been noted previously in cases of tuberculosis of the knee joint, and it evidently is caused by an increased blood supply and stimulation of growth at the epiphyseal cartilages. It was seen in the roentgenograms taken in these cases that the epiphyses of the femora and tibiae, as well as the patellae, were thicker than on the normal side.

Study of the roentgenograms of the twenty-four patients, in comparison with those of a series of proved cases of tuberculosis of the joints, shows that they have very little positive value in making the diagnosis. A definite diagnosis of arthritis was made from the roentgenograms in three cases, and two were thought to show nothing abnormal. The findings in the remainder were: effusion in the joint, thickening of the synovial membrane, thin joint space and decalcification of the bones. These are all found in synovial tuberculosis and therefore are valueless from the standpoint of differential diagnosis. The roentgen reports in five cases stated that the findings were consistent with, or suggested, tuberculosis.

The tuberculin test was positive in nine cases, doubtfully positive in three and negative in eight. In several of the earlier cases the Pirquet technic was used, but in the majority the Mantoux test was performed. In all cases in which a negative result was obtained, the test was repeated at least once. It would seem that a repeatedly nega-

tive intradermal test with both human and bovine tuberculin in a patient in good general condition is important and should be given much weight in making a diagnosis. Baldwin stated, however, that he would not exclude the possibility of an old tuberculous lesion, which may recently have become active, because of a negative Mantoux test.<sup>4</sup>



Fig. 1.—A section of a villus, showing round cell infiltration and dilatation of the blood vessels.

Previous experience with the quantitative test for the purpose of provoking a general and focal reaction had shown that it was of no value, for which reason it was not used in any of these cases.<sup>3</sup> The Wasser-

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4. Baldwin, Edward R. (Director of Trudeau Sanitarium): Personal communication to the author, Jan. 1, 1931.

mann or Kahn reactions were negative in the nineteen cases in which the tests were done.

The blood count was not particularly helpful in the diagnosis, although the average leukocyte count was higher than that in the normal or the tuberculous patient. There were fifteen counts above 8,000,



Fig. 2.—Higher magnification of an area from figure 1, illustrating clumping of the round cells about the blood vessels.

and only four of 8,000 or less. One patient whose condition was diagnosed as arthritis before operation had 19,500 leukocytes. The mononuclear cells were more than 30 per cent in twelve cases and less than 30 in six. The important point in this connection is that the blood count cannot be conclusive, and that it seldom is even suggestive.

Two knee joints were aspirated before operation, and the fluid was injected into guinea-pigs, with negative results. This procedure is no longer used generally, because the result cannot be learned for six weeks, because it is inconclusive when negative, and because it has been found that if tuberculosis is present, it usually can be discovered by immediate section of the tissue at the time of operation.

The operation in each case was done primarily as an exploration. One medial meniscus was removed because it was frayed, and three synovectomies were performed, including the case in which the cartilage was removed. Synovectomy was done subsequently in a fourth case in which symptoms recurred after four years. The incision used in every case was a median longitudinal one, parallel to the patella. By extending this upward a short distance above the patella, an excellent exposure can be had, and even the lateral portion of the joint can be seen fairly well. In several instances, a lateral incision also was made.

The appearance of the joints at operation is of special interest. In twenty-one cases the synovial membrane was greatly hypertrophied and tended to bulge out as soon as the capsule was divided. It was edematous and congested and varied in color from dark red to pale, dirty gray. In several cases it was almost gelatinous in appearance. The fluid in most cases was more abundant than in normal joints and usually was clear yellow. In a few instances coagulated lymph or fibrin was found in the joint. In the knee joints a pannus of varying size regularly was found growing over the margins of the articular cartilage of the femur. This conforms exactly to the picture seen in many cases of synovial tuberculosis.<sup>5</sup> It commonly was found that the thickened synovial membrane separated easily from the capsule, and that there was a distinct line of cleavage. Fibrosis with adhesions, but no suggestion of active disease, was found in two knees. The articular cartilage was well preserved in all except one knee, in which it was somewhat fibrillated.

Lipping at the margins of the joint caused the operator in two cases to decide from the gross appearance that he was dealing with chronic arthritis. Although the surgeon in each case had seen many tuberculous joints, he had the impression in sixteen cases that the lesion very probably was tuberculous, and in four others he was in doubt about its nature.<sup>6</sup> This again emphasizes the fact that no matter how

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5. Smith, A. DeF.: The Pathology of Joint Tuberculosis in Its Earlier Stages, *Arch. Surg.* **12**:740 (March) 1926.

6. Twelve patients were operated on by me and the remainder by three other members of the staff.

experienced a surgeon may be in such work, he usually cannot determine by the appearance of a joint alone what the nature of the lesion may be.

The picture presented in the sections of tissue from these joints varied from that of an acute to that of a chronic inflammatory process.



Fig. 3.—Diffuse infiltration of mononuclear cells. There is no thickening of the synovial layer.

In the large majority, there were hypertrophy of the villi, thickening of the surface layer of synovial cells and, underlying this, a greatly thickened subsynovial tissue. An exudate often was present on the surface. In nearly all cases there was some edema, and in a few this feature was very striking. The blood vessels were numerous and



dilated. The prevailing type of cell infiltrating the tissue was the small mononuclear, but in a few cases there also were numerous plasma cells. The lymphocytes were scattered diffusely through the tissue, but also were found in dense spherical clumps that bore no resemblance to tubercles. In six cases the round cells were massed about the blood

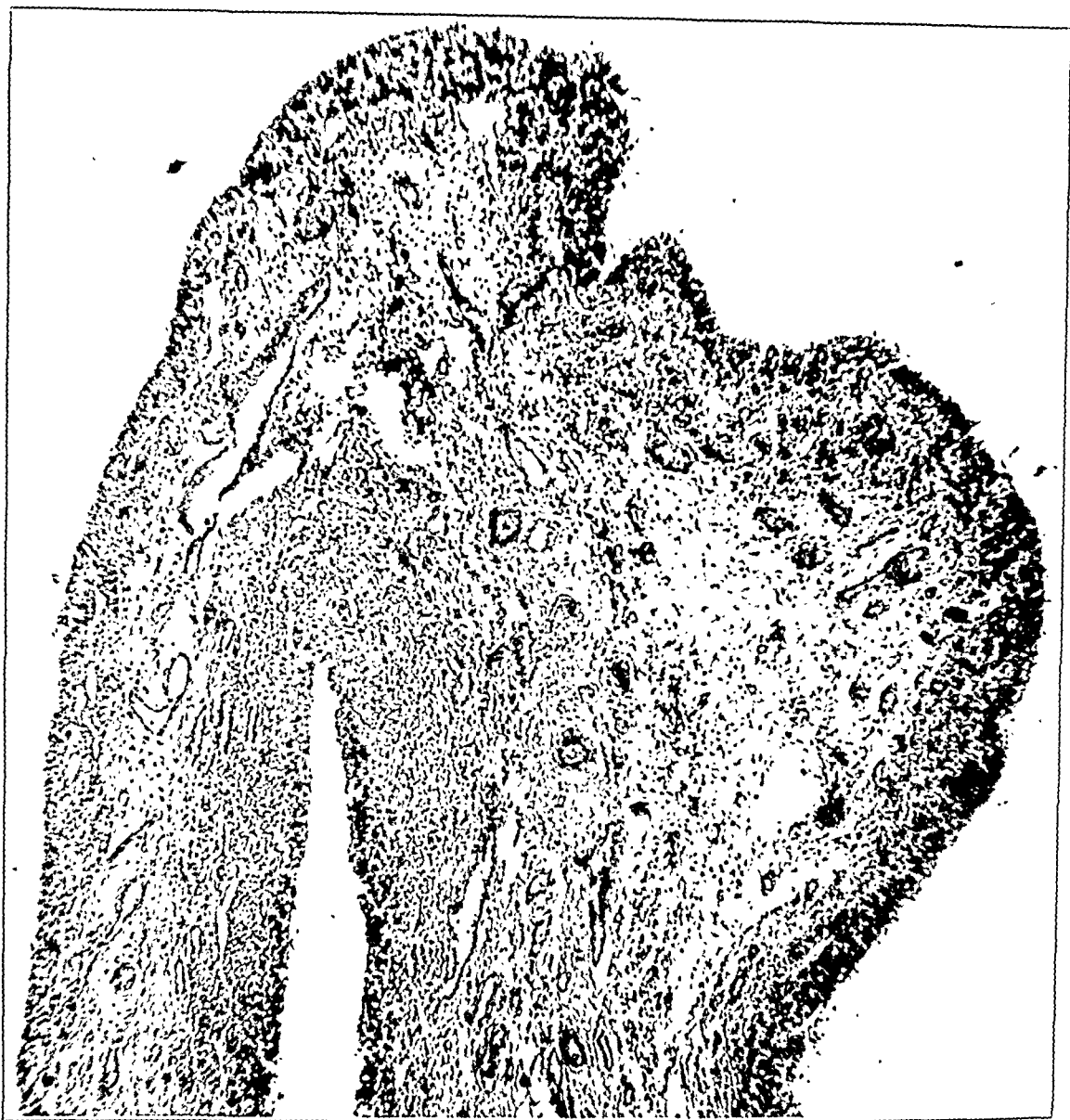


Fig. 4.—A thick synovial layer. There is an infiltration of cells immediately below the surface.

vessels in a manner that is said to be characteristic of syphilis, and indeed, the pathologist thought that there was a strong probability that these might be cases of syphilis. In all, however, the Wassermann reaction was negative, and there was nothing in the history or physical examination to corroborate this diagnosis. Obliterating endarteritis

was noted in one case. Polymorphonuclear cells were present in some cases, but were not numerous. Areas of necrosis and cloudy swelling of the adjacent regions were found in two examinations. The predominant feature of one case was well organized fibrous tissue with little infiltration of cells.

There is a record of cultures in seventeen cases. One resulted in a growth of *Staphylococcus aureus*. The onset of symptoms had been sudden, ten weeks previously, and while it was thought at operation

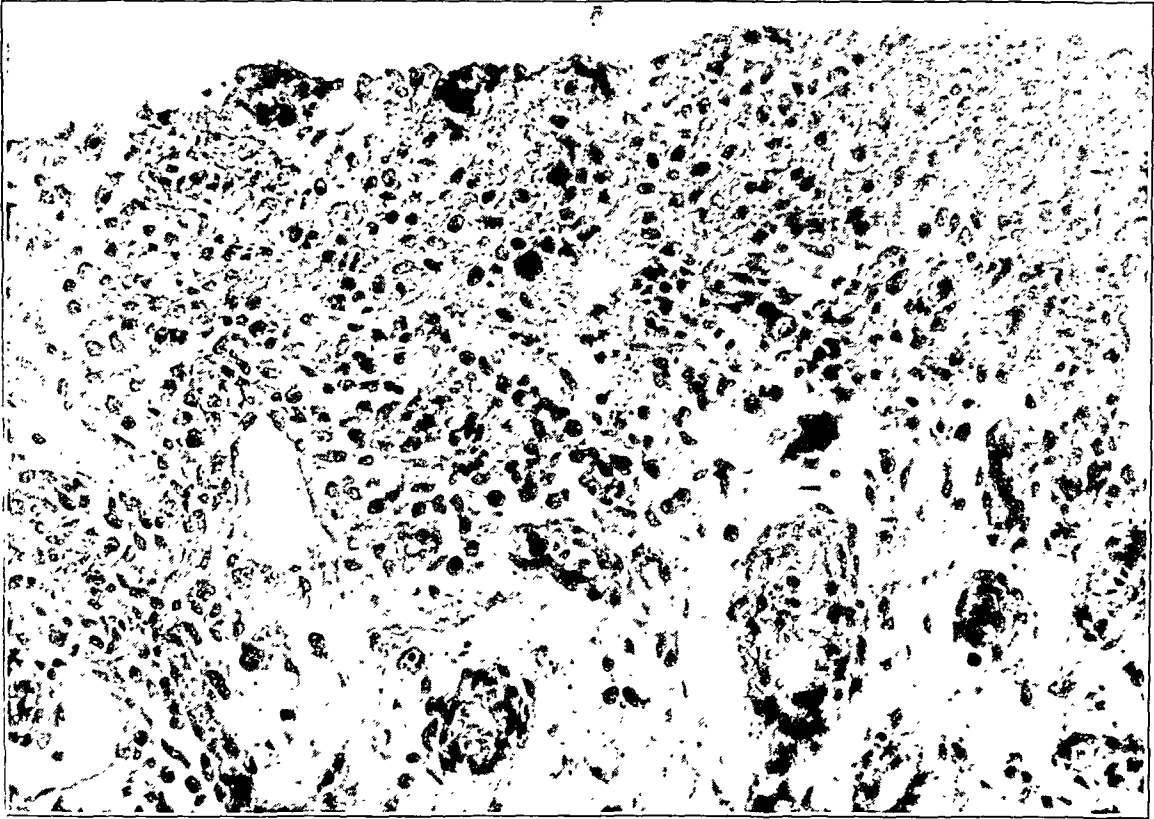


Fig. 5.—A small area of the section shown in figure 4, under higher magnification.

that the appearance was that of tuberculosis, there had been little doubt that the case was one of subacute arthritis. Culture in another case showed a growth of *Staphylococcus albus* and a gram-positive bacillus, which were considered contaminants. The others were all negative. In a great majority of cases, the tissue, as well as the fluid, was cultured on ordinary mediums, including agar slants and dextrose broth. It is certain that no results are to be expected in these cases except by special bacteriologic technic, and it is questionable whether organisms can be recovered from such joints at the stage when these operations

were done, although Cecil<sup>7</sup> recently reported growing streptococci in cultures from cases of arthritis. Tests on guinea-pigs with fluid or tissue, and often both, were done in twenty-two cases. The results in all were negative.

The behavior of these joints after exploratory operation was studied. One patient with arthritis of a hip subsequently developed symptoms in several joints and was treated with vaccines. He died of pneumonia thirteen months after operation. Four other patients later had symptoms in other joints, which would have simplified the diagnosis had they occurred earlier. A hip joint in which the bone of the femoral head and acetabulum both were affected became more and more stiff and painful until it finally was necessary to do an arthroplasty. A child whose symptoms and physical signs promptly disappeared after exploratory operation had no further trouble until marked swelling and effusion in the knee occurred four years later. A second operation was performed, revealing a greatly hypertrophied, congested, synovial membrane, which was excised. Swelling then disappeared, and a normal range of motion was obtained. An adult who was found to have a markedly hypertrophied, chronically inflamed, synovial membrane of the left knee was advised to have a synovectomy but refused. When last examined, his knee was still swollen and stiff. Of the remaining sixteen patients, fourteen have little or no stiffness, swelling or disturbance of function. In two the end-results are unknown.

#### REPORT OF CASES

The following two cases present typical histories:

CASE 1.—E. B., a girl, aged 3½ years, was first seen in the outpatient department of the New York Orthopaedic Dispensary and Hospital on Aug. 12, 1922. Her left knee became swollen and stiff and she began to limp following a fall from a chair in December, 1921. She was a well developed and nourished child who walked with a limp, owing to limitation of motion in the left knee. Physical examination gave negative results, except for the left lower extremity. The left knee was moderately swollen, and the patella floated. The thigh and calf were slightly atrophied. The temperature of the joint was slightly elevated. The leg could be extended to 180 degrees, but flexion was limited at 75 degrees by muscle spasm. Roentgen examination showed slight decalcification of the bones of the knee joint and effusion in the joint. On August 28, the joint was aspirated, and 15 cc. of blood-tinged fluid was obtained. This was cultured and injected into a guinea-pig. Culture was negative, and the guinea-pig failed to develop tuberculosis. In November, the physical signs persisted, and it was felt that in spite of the negative laboratory tests the joint probably was tuberculous. The parents were urged

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7. Cecil, Russell L.; Nichols, Edith E., and Stainsby, W. J.: Bacteriology of Blood and Joints in Chronic Infectious Arthritis, *Arch. Int. Med.* **43**:571 (May) 1929.

to allow the patient to go to the country branch of the New York Orthopaedic Hospital, but refused. A brace was applied. In June, 1924, there was atrophy of the thigh and calf, and the knee was slightly swollen. Motion was limited from 160 to 180 degrees. Roentgen examination showed general decalcification of the bones and enlargement of the patella and epiphyses. The brace was gradually discarded in September, 1924. In November, the Wassermann reaction was negative, as were Pirquet tests with both human and bovine tuberculin. Examination of the blood showed 4,480,000 red cells, 6,800 white cells and 52 per cent polymorphonuclears. In July, 1926, the patient injured the knee, and it became slightly more swollen. Slight crepitus was present, and flexion was limited to 80 degrees. Roentgen examination showed decalcification of the bones and synovial thickening without evidence of fluid. The Wassermann and Pirquet tests were repeated and gave negative results. By aspiration, 4 cc. of blood-tinged fluid was obtained. Cultures and tests on guinea-pigs gave negative results.

An exploratory operation was performed on the left knee on Oct. 5, 1926. The synovial membrane was hypertrophied and congested. A pannus extended over the medial condyle of the femur, but the bone and cartilage were not involved. Tissue was removed for section, culture and tests on guinea-pigs and the incision was closed. The incision healed by primary union. Early active and passive motion was begun, and convalescence was uneventful. Culture of this tissue was negative. Sections showed very marked, diffuse, round cell infiltration with numerous dilated blood vessels. On April 1, 1930, there was no swelling, limitation of motion or disturbance of function of the left knee. The left lower extremity was  $\frac{1}{4}$  inch (0.64 cm.) longer than the right.

CASE 2.—E. B., a man, aged 28, was admitted to the outpatient department of the New York Orthopaedic Hospital on Oct. 16, 1928. Two years previously he began to have swelling and stiffness in his left knee. There was no history of injury. Symptoms were intermittent, but the swelling never completely disappeared. No other joints were involved. Baking and diathermy were used, and plaster casts were applied twice. Recently he had been advised by another surgeon to have his knee operated on for removal of cartilage and "scraping of the bone." There was no history of pulmonary tuberculosis. The patient was a short, fairly well developed and nourished man. The tonsils were large and appeared infected. The teeth were in good condition. Physical examination otherwise gave negative results, except for the left lower extremity. The left knee was swollen and slightly warmer than the right. The patella floated. Motion was limited from 100 to 160 degrees by muscle spasm. There were 1 inch (2.5 cm.) atrophy of the thigh and  $\frac{3}{4}$  inch (1.87 cm.) atrophy of the calf, and the circumference of the knee was  $1\frac{1}{4}$  inches (3.14 cm.) greater than the right. Roentgenograms of the left knee showed a slight, dense, irregularly distributed effusion and a thin joint space, moderate decalcification and slight productive reaction, consistent with long-standing avirulent tuberculosis. Roentgen examination of the chest showed sclerotic nodes and moderate peribronchial infiltration, suggesting tuberculosis. The Mantoux test, with 0.05 mg. of tuberculin, was negative. The test was repeated, with 0.1 mg., with a strongly positive result. The Wassermann reaction was negative. Examination of the blood showed: white cells, 8,000; polymorphonuclears, 65 per cent; lymphocytes, 35 per cent.

The patient was sent to another hospital for removal of his tonsils. Examination of the tonsils gave negative results for tuberculosis. The patient was admitted to the New York Orthopaedic Hospital on Nov. 5, 1928, and an exploratory operation was done on November 9. The joint was exposed on the medial side. The

synovial membrane was thick, grayish and very soft and friable. The cartilage on the medial side of the femur was not eroded. A quantity of turbid fluid containing flakes of fibrin escaped. Pieces of synovial membrane were removed and were examined immediately by frozen section. The report was chronic inflammation, and the incision was closed, although it was believed from the appearance of the joint that the condition was tuberculosis. The sutures were removed in nine days, and the incision was healed. There was slight effusion, and motion was from 35 to 170 degrees. The patient was discharged on the eleventh day to await the guinea-pig test and further examination of the tissues. A culture of the fluid was sterile, and guinea-pigs inoculated with the fluid and tissue failed to develop tuberculosis. Permanent sections of the tissue showed immense numbers of blood vessels, some of which seemed to show thickening of the wall. There was a lymphocytic and plasma cell infiltration, occurring for the most part around the blood vessels, but seen in one or two areas as dense rounded masses. No necrosis or tubercle formation was seen. The diagnosis was changed to chronic arthritis of the left knee, and the patient was advised to have a synovectomy, but refused. When last seen, on Feb. 12, 1929, he still had swelling and limitation of motion of the knee.

#### CONCLUSIONS

1. Monarticular arthritis, which may simulate tuberculosis very closely, is not uncommon.
2. It is impossible to differentiate these lesions from those of tuberculosis by physical examination or the x-rays.
3. A repeatedly negative Mantoux test in such a case is suggestive but not conclusive.
4. Exploratory operation often is the only means of making the diagnosis, and even then the gross appearance of the joint is not to be relied on.
5. The histologic picture is that of a chronic inflammation. Cultures on ordinary mediums are negative.
6. The majority of the patients recover without further treatment.

# PRIMARY CARCINOMA OF THE GALLBLADDER

REPORT OF NINETEEN CASES \*

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AND

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The subject of primary carcinoma of the gallbladder may be considered to be of interest more from an academic than a clinical point of view. This statement is made because the disease is such that a preoperative diagnosis sufficiently early for successful surgical measures is practically impossible. Those few cases that have been reported in which cure was obtained are almost without exception those in which the carcinoma was found during an operation for some other condition, particularly gallstones. Even the greater majority of these were not diagnosed macroscopically but in the routine microscopic examination of gallbladders removed because of cholecystitis or cholelithiasis. In the only case among the 19 here reported in which the patient is still living, the carcinoma was not suspected during the operation but was found in the course of routine pathologic examination. The patient is still living and well six and one-half years after cholecystectomy which was done for cholecystitis and cholelithiasis.

Isolated cases of this disease were reported by de Stoll<sup>1</sup> in 1771, Hallé<sup>2</sup> in 1786 and Baillie<sup>3</sup> in 1793. However, the description by the latter coincided more nearly with the picture of tuberculosis. Frerichs<sup>4</sup> described the disease in 1858. Villard,<sup>5</sup> in 1869, collected 17 cases. Musser<sup>6</sup> collected 100 cases from the literature to 1889. From that date on, the cases reported become much more frequent. For other series of collected cases see the discussion of the relation between gallstones and carcinoma of the gallbladder.

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\* These nineteen cases comprise the total number found at operation and proved microscopically from 1916 to 1930 inclusive, at St. Luke's Hospital, New York.

1. de Stoll, quoted by Rolleston and McNee: *Diseases of the Liver, Gallbladder and Bile Ducts*, London, The Macmillan Company, 1929, p. 691.

2. Hallé: *Hist. Soc. de méd.*, Paris, 1786, p. 125.

3. Baillie, M.: *Morbid Anatomy*, London, J. Johnson, 1793, p. 158.

4. Frerichs, F. T.: *Diseases of the Liver*, translated by the New Sydenham Society, London, 1861, vol. 2, p. 479.

5. Villard: *Bull. Soc. anat. de Paris* **44**:217, 1869.

6. Musser, J. H.: *Boston M. & S. J.* **121**:528, 1889.

## INCIDENCE

*Sex Incidence.*—Rolleston and McNee<sup>7</sup> reported that from the Registrar General's returns in England and Wales from 1913 to 1920 there were 2,296 females and 946 males who died from malignant disease of the gallbladder, an incidence of 2.4:1. Ewing<sup>8</sup> calculated the relative incidence as 4 or 5:1; Schröder<sup>9</sup> as 5:1; Kaufmann,<sup>10</sup> Harley,<sup>11</sup> Kraus<sup>12</sup> and Colwell<sup>13</sup> as 2:1. Thirteen of our 19 cases were in females and 6 in males, an incidence just over 2:1. These figures correspond closely to the various estimates made as to the relative frequency of occurrence of gallstones in the two sexes.

*Age Incidence.*—Ewing<sup>8</sup> stated that carcinoma of the gallbladder occurs nearly always after the age of 40 and gave 58 years as the average age occurrence in both sexes. In our list the average age is 60.7, the youngest patient being 48 and the oldest 70. Moxon<sup>14</sup> reported a case of villous carcinoma of the gallbladder in a child 4 years of age. Proescher<sup>15</sup> reported a case in a man 22 years old. Kaufmann,<sup>10</sup> Haas<sup>16</sup> and Chavannaz<sup>17</sup> each reported a case in a patient 25 years of age. Thomas and Noica<sup>18</sup> reported a case in a patient 90 years old. Kaufmann<sup>10</sup> mentioned a woman, aged 95, who had carcinoma of the neck of the gallbladder with a stone. Haberfeld<sup>19</sup> stated that the oldest patient he found was a man, aged 93, whose case was reported by Riedel.<sup>20</sup>

*Incidence in Relation to Gallstones.*—This subject will be discussed fully in the discussion of etiology.

*General.*—Carcinoma of the gallbladder is usually given fifth place in frequency of incidence among the organs concerned with digestion.

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7. Rolleston and McNee: *Diseases of the Liver, Gallbladder and Bile Ducts*, London, The Macmillan Company, 1929, p. 691.

8. Ewing, James: *Neoplastic Diseases*, Philadelphia, W. B. Saunders Company, 1928, p. 736.

9. Schröder, quoted by Naunyn: *On Cholelithiasis*, translated by the New Sydenham Society, London, 1896, p. 38.

10. Kaufmann, Edward: *Pathology*, Philadelphia, P. Blakiston's Son & Company, 1929, vol. 2, p. 1002.

11. Harley, G.: *Diseases of the Liver*, London, J. & A. Churchill, 1883, p. 575.

12. Kraus, J.: *On Gallstones*, English translation, London, Kegan & Paul, 1896, p. 2.

13. Colwell, H.: *The Relation of Carcinoma to Gallstones*, Arch. Middlesex Hosp., London 5:123, 1905.

14. Moxon: Tr. London Path. Soc. 18:140, 1868.

15. Proescher, F.: *A Remarkable Case of Carcinoma of the Gallbladder in a Man Twenty-Two Years Old*, J. A. M. A. 48:481 (Feb. 9) 1907.

16. Haas, H.: Prag. Vitljhrschr. 132:136, 1876.

17. Chavannaz: Gaz. hebdomadaire de médecine, Paris 6:721, 1901.

18. Thomas, A., and Noica: Bull. Soc. anat. de Paris 71:471, 1896.

19. Haberfeld: Ztschr. f. Krebsforsch. 7:190, 1908.

20. Riedel: Berl. klin. Wchnschr. 38:1, 1901.

The incidence is: (1) stomach, (2) colon (and cecum), (3) rectum, (4) esophagus and (5) gallbladder and ducts. Kaufmann<sup>10</sup> estimated carcinoma of the gallbladder as making up 5 per cent of all carcinoma found at autopsy. Smithies<sup>21</sup> found among 1,000 consecutive cases of gallbladder disease 23 cases of primary and 8 of secondary malignant disease. McCarty,<sup>22</sup> in a survey of 4,998 gallbladders removed at operation, found only 24 cases of carcinoma. Sherrill<sup>23</sup> and others reported that carcinoma is the most common tumor of the gallbladder.

#### PATHOLOGY

*Histology.*—Ewing<sup>8</sup> classified primary carcinoma of the gallbladder into the following groups according to the gross anatomy: (1) villous, papillomatous or fungating, (2) gelatinous and (3) diffuse, flat or infiltrating carcinoma.

As to the structural anatomy, he classified the types as follows: (1) adenocarcinoma, (2) alveolar carcinoma and (3) squamous cell carcinoma, either pure or associated with cylindric cell carcinoma.

Rolleston and McNee<sup>7</sup> classified carcinoma of the gallbladder histologically as columnar or spheroidal cell carcinoma, and stated that the cells may undergo colloid degeneration. The columnar cell carcinoma may grow into the cavity of the gallbladder as a villous tumor or a papilloma. Delafield and Prudden<sup>24</sup> and Treutlein<sup>25</sup> described the structure in the same manner. Rolleston and McNee<sup>7</sup> stated that in invasion of the deeper layers it does not show a papillary arrangement, but that ordinarily it is a columnar cell carcinoma with a fair amount of fibrous tissue. The cells of part of the growth may be columnar, of part cubical and of part spheroidal.

The large epithelial cells may even appear flattened. Multinuclear cells are seen at times. They added that as a result of metaplasia a squamous cell carcinoma of the gallbladder may occur and they collected 36 cases from the literature up to 1929. Similar cases have been described by Herxheimer,<sup>26</sup> Lubarsch,<sup>27</sup> Nicholson<sup>28</sup> and Simmonds.<sup>29</sup> Infiltration of the wall may occur without any villous projection into

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21. Smithies, F.: *Am. J. M. Sc.* **157**:67, 1919.

22. McCarty, W. C.: *Ann. Surg.* **69**:131, 1919.

23. Sherrill, J. G.: *Ann. Surg.* **44**:866, 1906.

24. Delafield, F., and Prudden, T. M.: *Pathology*, New York, William Wood & Company, 1927, p. 861.

25. Treutlein, A.: *Centralbl. f. allg. Path. u. path. Anat.* **12**:825, 1901.

26. Herxheimer: *Beitr. z. path. Anat. u. z. allg. Path.* **41**:348, 1907.

27. Lubarsch, O.: *Verhandl. d. deutsch. path. Gesellsch.* **10**:198, 1906; *Die Metaplasiefrage und ihre Bedeutung für die Geschwulstlehre*, *Arb. a. d. path. anat. Abt. d. k. hyg. Inst. zu Posen*, 1901, p. 205.

28. Nicholson, G. W.: *Path. & Bact.* **13**:41, 1909.

29. Nicholson, G. W.: *J. Path. & Bact.* **13**:41, 1909.



the lumen of the gallbladder. Because of this the tumors are grouped as follows: (1) villous or papillomatous, (2) infiltrating and (3) gelatinous.

The latter is an infrequent form, usually filling the lumen of the gallbladder, and in women it may involve the ovaries by extension giving rise to one type of the so-called Krukenberg bilateral ovarian carcinoma.<sup>30</sup>

*Site of Origin.*—Rolleston and McNee<sup>7</sup> stated that one would conclude that carcinoma of the gallbladder arises from three locations, according to the descriptions of the earlier cases:

1. The fundus. It is the most dependent portion of the gallbladder and therefore particularly exposed to irritation from calculi.

2. The midportion. This produces the so-called hour-glass gallbladder.

3. The neck. Stones are often found impacted here.

However, the greater number are found involving the gallbladder so extensively that the site of origin cannot be definitely determined.

*The Gallbladder.*—Kaufmann<sup>10</sup> stated that the gallbladder is usually found distended, hydropic or filled with pus. It contains calculi in a large percentage of cases. Rarely the entire wall is infiltrated, forming a tumor the size of a fist or larger, containing stones and with very little of the gallbladder wall remaining. The carcinomatous gallbladder may shrink to a mass the size of a bean with its cavity containing calculi.

*Extension.*—Extension may occur by two methods: direct growth into the liver or by adhesions to any adjacent structure. It may grow into and along adjacent blood vessels.

By metastasis it may spread to the liver, giving scattered nodules. Rolleston and McNee<sup>7</sup> mentioned a case with white nodules of carcinoma in the serosa of the small intestine. Kaufmann<sup>10</sup> stated that metastases to the pouch of Douglas may predominate the picture, that metastasis to the regional lymph nodes is rare and that he has seen metastasis to the lung. Osler<sup>31</sup> reported a case with metastasis to the right breast. However, distant metastases are only rarely mentioned. Involvement of the liver was noted in 10 of our 19 cases, of the lymph nodes along the common duct in 8, of the peritoneum in

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30. Krukenberg, F. E.: Arch. f. Gynäk. **50**:287, 1895-1896. Metzger, M. Leo: Metastases ovariques des cancers digestifs, Thèse, Paris, 1911, no. 354. Hall, M. E.: Proc. New York Path. Soc. **12**:57, 1912. Stone, W. S.: Surg., Gynec. & Obst. **22**:407, 1916. Major, R. H.: ibid. **27**:195, 1918. Delafield and Prudden (footnote 24).

31. Osler, W.: Brit. M. J. **1**:2, 1906.

2, of the colon in 1, of the bladder in 1 and of the lymph nodes along the aorta in 1.

*Fistulas.*—Perforation may occur into the colon, stomach or duodenum. Perforation into the colon occurred in 10 of the 100 cases collected by Musser.<sup>6</sup> Of Riedel's<sup>32</sup> 100 cases, 6 showed the same condition, perforation occurring into the stomach in 5 and into the duodenum in 10. One of our cases showed an old perforation into the colon.

Rolleston and McNee<sup>7</sup> called attention to the fact that this not infrequently occurs in cholelithiasis, so that in at least a part of these cases the perforation may well have occurred before the carcinoma developed.

*Pressure Effects.*—These effects may be classed into two groups. Pressure against the duodenum may be such that the findings simulate carcinoma or other stricture of the pylorus. Rabé and Rey<sup>33</sup> and Lejonne and Melanoff<sup>34</sup> reported this condition. One of our patients had definite duodenal obstruction due to pressure. In another, the colon was obstructed but only partly.

Closure of the portal vein and its associated group of findings may be caused either by pressure or by direct invasion of the vein. This was found as the etiologic factor in 6 of 68 cases of pylephlebitis collected by Lissauer.<sup>35</sup> In 2 of our cases there was definite obstruction of the hepatic duct due to the pressure of metastases. In another there was apparently intermittent obstruction of the cystic duct causing recurrent enlargement of the gallbladder, but this may have been caused by the contained stones.

#### ETIOLOGY

*Relation of Carcinoma (At Any Site in the Body) to Gallstones.*—This subject is slightly aside from the one under discussion but is of interest indirectly and is mentioned in order to discuss what appears to us to be an apparently mistaken assumption.

Colwell,<sup>13</sup> in 1905, reported the following: Among 11,400 autopsies from 1854 to 1899 at the Middlesex Hospital, gallstones occurred in 359, or 3 per cent. Among 1,886 autopsies from 1900 to 1904, gallstones were found in 102, or 5.7 per cent. Colwell's figures from 1854 to 1904 for the relative occurrence of gallstones in cases of carcinoma (at any site in the body) in the two sexes were approximately proportional to the liability of males and females to cancer. In the autopsies from 1900 to 1904, gallstones were found in both sexes

32. Riedel: München. med. Wchnschr. **58**:1337, 1911.

33. Rabé and Rey: Bull. Soc. anat. de Paris **72**:881, 1897.

34. Lejonne and Melanoff: Bull. Soc. anat. de Paris **75**:133, 1900.

35. Lissauer: Virchows Arch. f. path. Anat. **192**:278, 1908.

approximately two and one-half times as frequently in carcinomatous as in noncarcinomatous cases. At first glance this would suggest that the occurrence of cancer at any site in the body predisposes that person for some reason to the formation of gallstones. However, as the age incidence of gallstones and cancer falls within much the same limits, this seeming direct relation probably is only incidental.

*General.*—In summing up the factors concerned in the etiology of carcinoma of the gallbladder, Ewing<sup>8</sup> stated that the following combine in producing the remarkable susceptibility of the mucous membrane of the gallbladder to the formation of carcinoma: (1) mechanical irritation of calculi, (2) catarrhal inflammation that excites a cellular overgrowth, (3) the relation to a peculiar form of lipid metabolism (cholesterol) and (4) irritative and digestive action of the bile.

*Relation to Gallstones.*—The occurrence of gallstones in carcinomatous gallbladders is unquestionably greater than that in noncarcinomatous gallbladders. Of course, the question arises as to whether or not the stones form after the carcinoma, but in a great many cases the history of cholecystitis and cholelithiasis precedes the most remote time at which the carcinoma might have originated. Those authors favoring the theory that carcinoma is the cause of the increased incidence of stones state that the growth favors infection, stagnation and cholecystitis, and consequently the formation of stones.

However, if this were entirely correct, the incidence of stones should be approximately the same in primary and secondary carcinoma of the gallbladder. As against this, Siegert<sup>36</sup> collected 99 cases of primary carcinoma of the gallbladder with stones in 94. In his 13 cases of secondary carcinoma of the gallbladder stones were found in only 2. Rolleston and McNee<sup>7</sup> reported 25 additional cases of secondary carcinoma of the gallbladder with stones found in only 1. This gives an occurrence of stones in cases of secondary carcinoma of the gallbladder of 8 per cent, which is within the limits of the expectance of gallstones. (Schröder<sup>9</sup> estimated that from 5 to 12 per cent of all autopsies done as a routine measure show gallstones.) Of course, secondary carcinoma ordinarily occurs under the mucosa while primary carcinoma is in the lumen of the gallbladder and would therefore be a more important factor in the production of stones.

In Schröder's<sup>9</sup> 120 cases of gallstones there were 20 cases of primary carcinoma of the gallbladder (14 per cent). Fawcett and Rippmann<sup>37</sup> reported 592 cases of gallstones from the postmortem records of Guy's Hospital with 48 cases of carcinoma of the gallbladder and cystic duct (12.3 per cent). Riedel<sup>32</sup> estimated that from 7 to 8 per

36. Siegert, F.: Virchows Arch. f. path. Anat. **132**:353, 1893.

37. Fawcett, J., and Rippmann, C. H.: Guy's Hosp. Rep. **67**:41, 1913.

cent of cases of cholelithiasis showed carcinoma. Rolleston and McNée<sup>7</sup> reported 300 cases of gallstones from St. George's Hospital with 13 cases of carcinoma (4.3 per cent), but they stated that among the 300 cases were included many showing only minute bilirubin calcium stones and gave this as the reason for the low incidence.

Slade<sup>38</sup> found carcinoma in 10 cases among 17 gallbladders (59 per cent) with chronic inflammatory changes associated with gallstones; all but 1 of the patients had died from the effects of the gallstones. In 5 of these the carcinoma could be demonstrated microscopically only.

In patients with mental disease (i. e., in patients brought into the hospital always for some reason other than symptoms referable to the gallbladder or to cancer), Candler<sup>39</sup> found only 2 cases of primary carcinoma of the gallbladder in 315 cases of gallstones (less than 1 per cent). The implication in this is that those patients with gallstones and cancer, being more seriously ill, are taken to hospitals, and the incidence in the hospitals is thus increased far beyond the actual incidence in the general population.

Approaching the question from the other side, we have the following figures on the incidence of gallstones in cases of carcinoma of the gallbladder. In 14 of our 19 cases stones were noted (73.7 per cent). They ranged in number from a solitary stone to more than 60. In some of the cases only a cholecystostomy or biopsy was done, and at least a part of these may have had unnoticed stones.

The incidence in various groups of collected cases is as follows:

#### *Incidence of Stones*

	Number of Cases	Percentage With Stones
Musser <sup>6</sup> .....	100	60
Fütterer: Ueber die Aetiologie des Carcinomas, Wiesbaden, J. F. Bergmann, 1901, p. 55; Festschr. f. G. E. von Rindfleisch, Leipzig, 1907, p. 89.....	268	70
Haberfeld <sup>10</sup> .....	190	70
Zenker: Deutsches Arch. f. klin. Med. 44: 159, 1888-1889.....	159	55
Courvoisier: Pathologie und Chirurgie der Gallenwege, Leipzig, F. C. W. Vogel, 1890, p. 375.....	103	91
Siegert <sup>20</sup> .....	...	95
Janowski: Beitr. z. path. anat. u. z. allg. Path. 10: 449, 1891.....	...	100

There is undoubtedly some duplication of cases in part of these compilations. The incidence, however, is great enough to suggest a definite relationship between the irritation of the calculi, the associated cholecystitis and the carcinoma formation.

Erdmann<sup>40</sup> reported that in a series of 224 consecutive operations for cholecystitis 15 cases showed carcinoma of the gallbladder. In 1,000

38. Slade: *Lancet* 1:1059, 1905.

39. Candler: *Proc. Roy. Soc. Med.* 4:87, 1911.

40. Erdmann, J. F.: *Am. J. Obst.* 80:618, 1919.

operations for gallstones, Deaver<sup>41</sup> found malignancy in 16. Smithies<sup>21</sup> reported 23 in 1,000 operations on the gallbladder. Schnabel<sup>42</sup> reported a case in which carcinoma of the gallbladder developed long after an incomplete cholecystectomy. Coates<sup>43</sup> reported a case in which carcinoma of the gallbladder developed seven years after a calculus was removed.

Lazarus-Barolow<sup>44</sup> put forth a unique idea. He reported that calculi removed from patients with carcinoma of the gallbladder contained more radioactive materials than other gallstones. In the literature we could find no confirmation of this finding.

Leitch,<sup>45</sup> in 1924, produced carcinoma in the gallbladder of guinea-pigs experimentally by inserting human gallstones, pebbles and pitch into the gallbladder. In a small series of cases the incidence of carcinoma formation was greater with the pebbles or pitch. He stated that this was the first time glandular carcinoma had been developed experimentally. Debbet and Godard,<sup>46</sup> in 1928, reported having produced carcinoma by inserting gallstones from cancerous human gallbladders into the gallbladders of guinea-pigs.

One of us (Dr. Shelley) recently reported a case in which a good-sized piece of tape had remained in a patient's gallbladder for a period of eighteen years. Careful microscopic examination of this gallbladder revealed no carcinoma cells.

#### CLINICAL PICTURE

Rolleston and McNee<sup>7</sup> stated that the symptoms of carcinoma of the gallbladder may be referred to: (1) a preexisting cholelithiasis and cholecystitis, (2) the local effects of the carcinoma in the gallbladder and (3) the more distant effects due to extensions and metastases—to which should be added the general or constitutional effects of malignancy.

Ewing<sup>8</sup> stated that the initial symptoms may be local pain or dyspepsia, but that a local tumor is the first symptom in 50 per cent of the cases. He stated also that jaundice suddenly established and persistent occurs in most cases, although some authors do not give this symptom such prominence. Ascites is often added from throm-

41. Deaver, J. B., and Ashhurst, S. P. C.: *Med. Rec.* **96**:47, 1919; *Surgery of the Upper Abdomen*, ed. 1, Philadelphia, P. Blakiston's Son & Company, 1909, p. 218; *Am. J. Surg.* **38**:105, 1924.

42. Schnabel, T. G.: *Am. J. M. Sc.* **162**:95, 1921.

43. Coates, H. W.: *Clinical Hour* **58**:54 (Jan. 30) 1929.

44. Lazarus-Barolow, W. S.: *Brit. M. J.* **1**:95, 1914.

45. Leitch, A.: *Brit. M. J.* **2**:451, 1924.

46. Debbet, Paul; and Godard, H.: *Bull. Assoc. franç. p. l'étude du cancer* **17**:347 (June) 1928.

basis of large veins or peritoneal metastases, and the effusion may be chylous. He added that the cachectic stages are marked by fever from infections, cholemia, hemorrhages and emaciation. The total duration is extremely variable, some cases never being suspected until autopsy. After the appearance of jaundice few patients live more than six months.

There may or may not be a history of attacks of gallstone colic and cholecystitis. Kehr<sup>47</sup> found the symptoms of gallstones absent in the majority of his cases. Jourdan<sup>48</sup> reported a case in which there was a history of colics for twenty-five years before the carcinoma was found. Bret<sup>49</sup> reported the case of a woman who died at the age of 36 of carcinoma of the gallbladder which contained an oval calculus. She had had gallstone colics for the sixteen preceding years. Many patients found to have carcinoma of the gallbladder have had no symptoms of gallstones, but, of course, many patients are found to have gallstones who have never had symptoms. Magoun and Renshaw<sup>50</sup> reported that in their 84 cases they found that the duration of symptoms ranged from one month to forty years. The average loss of weight was 15 pounds (6.8 Kg.), the greatest 50 pounds (22.7 Kg.). Sixty patients gave a definite history of gallstone colic. Thirty-two complained of a dull pain with or without colic. Forty patients had varying degrees of jaundice. Twenty-three gave a history of fever.

Rolleston and McNee<sup>7</sup> described the course of a typical case having symptoms as follows: If there is a history of colics or cholecystitis, there is no change in the clinical picture at the onset of the growth. Later, continuous pains, a hard, rough gallbladder continuously increasing in size, and the general symptoms of a malignant condition may appear.

Cases are not uncommon in which no symptoms had pointed to the gallbladder as the source of a patient's metastatic carcinoma. Osler<sup>31</sup> reported a case of carcinoma of the right breast found later to be a metastasis from a primary carcinoma of the gallbladder. Two cases are reported by Rolleston and McNee<sup>7</sup> from St. George's Hospital, one a case with ascites and no jaundice diagnosed as cirrhosis of the liver. At autopsy, a primary carcinoma of the gallbladder was found containing stones. Metastases to glands behind the pancreas had compressed the portal vein, causing ascites. The second case showed a metastatic growth in the spine simulating caries. Later, a carcinoma of the gallbladder was found to be the source.

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47. Kehr: *Diagnosis of Gallstone Disease*, Philadelphia, 1901, p. 92.

48. Jourdan: *Bull. soc. anat. de Paris* 66:323, 1891.

49. Bret: *Lyon méd.* 89:35, 1898.

50. Magoun, J. A. H., Jr., and Renshaw, K.: *Ann. Surg.* 74:700, 1921.

Symptoms referable to gallstones in our 19 cases are: Only 5 patients gave a history of typical gallstone colics; 2 gave a history of milder but more continuous pain in the right upper quadrant of the abdomen referred to the right shoulder and 2 had had chills and fever. Local symptoms referable to the tumor are: jaundice in 8 cases, pain in the right upper quadrant in 8 and palpable tumor in 9. The only general symptom of carcinoma was loss of weight as noted in 8 cases, the greatest amount being 25 pounds (11.3 Kg.), and one case with marked loss of strength.

*Symptoms of Liver Invasion.*—The symptoms due to invasion of the liver are the same as those of any other cancerous invasion of the liver. It may be enlarged. The surface is smooth or nodular, according to the type of involvement. The bile ducts may become involved with jaundice resulting. The various groups of collected cases show jaundice in from 60 per cent up, although in a part of these it was found to be due to some associated condition, such as stones in the hepatic or common ducts and cholangitis. Jaundice was present in 8 of our cases, in 2 of which there were common duct stones.

*Distant Effects.*—The more distant effects are those of any malignancy—*anemia*, *cachexia* and the like. It is very interesting to note that among the 9 cases in our list in which hemoglobin determinations and red counts were made, 7 showed normal findings, 1 slight anemia, and only 1 a severe anemia. Judd and Baumgartner<sup>51</sup> also noted that anemia is almost never associated with malignancy of the gallbladder.

Ascites due to peritoneal implants or obstruction of the portal vein is not uncommon. Secondary growths may cause obstruction of the pylorus or colon. Breaking down of the carcinoma tissue may cause perforation or abscess formation. Ascites was noted as present in 2 and loss of weight and cachexia in 8 of our cases.

#### DIAGNOSIS

In a large percentage of cases the diagnosis of carcinoma of the gallbladder cannot be made without direct examination by operation. A great many are never suspected and are found only at autopsy. Ordinarily, when a positive diagnosis can be made preoperatively, it is too late to operate.

The condition should be suspected in a patient with a history of gallstone colics or attacks of cholecystitis who has a continuous and increasingly severe pain in the epigastrium or the right side of the

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51. Judd, F. S., and Baumgartner, C. J.: Malignant Lesions of the Gallbladder, *Arch. Int. Med.* **44**:735 (Nov.) 1929.

hypochondrium, loss of appetite and a nodular tumor increasing in size in the location of the gallbladder.

*Roentgen Examination.*—A positive diagnosis can be made if the outline of the tumor shows with the dye in a roentgenogram. Failure of the gallbladder to fill is suggestive and is the most common finding. Graham and Cole,<sup>52</sup> Whitaker, Milliken and Vogt<sup>53</sup> and Carman<sup>54</sup> concur in this. Cholecystograms were made in but 2 of our cases, and in both the gallbladder did not fill.

Kirklin<sup>55</sup> reported 20 cases with a diagnosis of papilloma of the gallbladder, in 4 of which operation was performed and the diagnosis confirmed. He found that papillomas have definite roentgenologic characteristics: The shadows retained the same position in all films in which they appeared. The small round defects were never more than 1 cm. in diameter, and never immediately at the fundal pole, but often were marginal. The defects might be single or might be three or more, but they were always discrete. Frequently the defects were clear and usually most clearly visible at the twentieth hour after oral administration of the dye. He hoped that this finding might aid in the diagnosis of carcinoma of the gallbladder in its earlier stages.

#### DIFFERENTIAL DIAGNOSIS

*Gallstones and Cholecystitis.*—The symptoms of carcinoma of the gallbladder and gallstones and cholecystitis are much the same, and often the symptoms of cancer are merely grafted onto those of a pre-existing diseased condition of the gallbladder. A very thick, chronically inflamed gallbladder wall may look like carcinoma even when opened and examined. Dense adhesions in the right upper quadrant are found in both conditions. Stones in the common duct may feel like glands invaded by carcinoma. Microscopic examination at times reveals carcinoma in a gallbladder wall removed for some other condition and not previously suspected.

*Malignant Disease of the Liver.*—Primary malignant disease of the liver or carcinomatous metastasis, whether from the gallbladder or

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52. Graham, E. A., and Cole, W. H.: Roentgenologic Examination of Gallbladder, New Method Utilizing Intravenous Injection of Tetrabromphenolphthalein, J. A. M. A. **82**:613 (Feb. 23) 1924. Graham, E. A.; Cole, W. H., and Copher, G. H.: Visualizing of Gallbladder by the Sodium Salt of Tetrabromphenolphthalein. *ibid.* **82**:1777 (May 31) 1924.

53. Whitaker, L. R.; Milliken, G., and Vogt, E. C.: Surg., Gynec. & Obst **40**:847, 1925.

54. Carman, R. D.: Lancet **2**:67, 1925.

55. Kirklin, B. R.: Proc. Staff. Meet., Mayo Clin. **5**:336 (Nov. 19) 1930; Cholecystographic Diagnosis of Papillomas of the Gallbladder. Am. J. Roentgenol. **25**:46 (Jan.) 1931.



other sources, presents the same picture. A preceding history referable to the gallbladder suggests that organ as the origin of the growth.

*Carcinoma of the Stomach.*—Carcinoma of the gallbladder may cause pyloric obstruction by pressure. A barium sulphate meal and roentgenograms may differentiate the causes of the obstruction. There should be a difference in the early history of the two conditions.

*Carcinoma of the Hepatic Flexure of the Colon.*—Invasion of the colon by the carcinoma of the gallbladder may give the same symptoms as carcinoma of the colon. The previous history together with roentgen examinations of the stomach, gallbladder and colon may differentiate the two.

*Carcinoma of the Head of the Pancreas and Bile Ducts.*—Late in the disease the similarity between this condition and carcinoma of the gallbladder is so close that it is often impossible to differentiate them. Also both may have been preceded by a history typical of gallstones or cholecystitis.

*Syphilis.*—Syphilitic disease of the liver, particularly with a gumma in the region of the gallbladder, may give much the same picture as carcinoma of the gallbladder. A positive Wassermann reaction, of course, does not rule out carcinoma, nor a negative one syphilis.

*Other Conditions.*—Gerhardt<sup>50</sup> reported a case in which from scar contraction and deformity a piece of the right lobe became elongated and hard so that during life it was thought to be a carcinoma of the gallbladder.

#### TREATMENT

*Prophylactic.*—Removal of gallbladders from patients who have a history of gallstone colics or attacks of cholecystitis and of those in whom stones are found accidentally may prove to be of value in the prevention of the development of carcinoma of the gallbladder. Judd and Baumgartner<sup>51</sup> stated that at the Mayo Clinic the frequency of the occurrence of malignant disease of the gallbladder had diminished from 5 per cent in the earlier years to 0.5 per cent in later years. They attributed this to the fact that diseased gallbladders are now removed much earlier.

*Medical.*—Medical treatment is only palliative and is used in relieving the symptoms as they arise. Roentgen treatment may relieve some of the symptoms temporarily.

*Surgical.*—Surgical removal presents the only hope of cure at the present time, but diagnosis is nearly always made so late that an attempt at complete removal cannot be made. Except in the rare cases in which the growth is very small and limited to the free portion of the gallbladder wall, the operative mortality is very high. In many cases

56. Gerhardt: *Semaine méd.* 18:273, 1898.

attempted removal is contraindicated, but various surgical procedures to relieve conditions caused by the growth may be indicated.

#### PROGNOSIS

The various reports of percentages of surgical cures varies from none to 6 per cent. Fourteen of our patients died in the first three weeks after operation. Of the remaining 5, 1 died in one month, 3 died at six months of metastases and 1 is living and well at six and one-half years.

Quinn<sup>57</sup> collected 57 cases in which carcinomatous gallbladders had been removed. Fifty of the patients died within a year. This includes the immediate operative mortality. Two died at the end of a year. Five were reported living, 1 at eight months, 1 at two years and two months, 2 at three years and 1 at four years and six months. Magoun and Renshaw<sup>50</sup> reported a series of 84 cases in which operation disclosed malignancy of the gallbladder. The operative mortality was 8, just under 10 per cent. Of the 29 patients on whom only explorations were done and who were later traced, the greatest length of life was three years. Of the 26 on whom cholecystectomy was done and who were later traced, 6 were still alive, 3 at two years, 1 at eight years, 1 at nine years and 1 at eleven years. The last showed the greatest length of life for the group. Twelve did not live longer than a year. The remaining deaths were fairly evenly divided among the years to eleven.

Webber,<sup>58</sup> in reporting 30 cases of primary carcinoma of the gallbladder in 1927, classified them into four grades according to the differentiation of the carcinoma cells. Two patients, both with grade II carcinoma, were still living at the time the report was made, 1 at thirteen months and the other at seventy-nine months. The average lengths of life of patients with grade I carcinoma was sixteen months; with grade II, ninety-two and three-tenths months; with grade III, seven and five-tenths months; with grade IV, thirteen months. Webber concluded that determination of the grade of malignancy through a study of the cell differentiation in a microscopic section of the tumor appeared to be a definite aid in estimating both the likelihood of metastasis and the relative length of life of the patient after operation.

Even in those cases in which the growth at the time of removal was very small, early and extensive recurrence and metastases are frequently the outcome. Heidenhain<sup>59</sup> removed a gallbladder containing six stones. A button-like thickening on the gallbladder wall proved to be carcinoma, microscopically. The patient died of metastases in the liver three months

57. Quinn, M.: *Bull. et mém. Soc. d. chirurgiens de Paris* **34**:215, 1908.

58. Webber, I. M.: *Surg., Gynec. & Obst.* **44**:756 (June) 1927.

59. Heidenhain: *Verhandl. d. deutsch. Gesellsch. f. Chir.*, 1898, p. 126.

later. At the time of operation the liver had been found smooth. One of our cases was similar to this in every detail.

#### REPORT OF CASES

CASE 1.—Mrs. E. R., white, aged 64, a housewife, entered the hospital on Jan. 10, 1916, because of acute severe pain in the right upper quadrant. The white cell count was 29,000, with polymorphonuclear leukocytes 82, and lymphocytes 18.

Operation revealed a gangrenous gallbladder connected with the transverse colon by a fistulous opening. There were many stones in the gallbladder, and one was removed from the common duct. The gallbladder was removed.

Microscopic examination showed carcinoma of the gallbladder which was acutely infected and contained areas of gangrene.

The patient died a few hours after operation.

CASE 2.—Mr. J. F., white, aged 65, no occupation, entered the hospital on Jan. 12, 1916, because of pain in the right upper quadrant. Operation revealed a thickened gallbladder containing stones. A diagnosis of carcinoma was made and cholecystectomy done. There were many adhesions about the cystic duct, probably due at least in part to extension of the carcinoma. Microscopic examination confirmed the diagnosis of carcinoma.

The patient was discharged on the sixteenth day after operation with the wound healed, but died six months later of metastases.

CASE 3.—Mr. N. M. L., white, aged 53, a physician, entered the hospital on Jan. 12, 1916, because of pain in the right upper quadrant. Operation revealed the gallbladder a solid mass of carcinoma and the entire liver riddled with metastases. A piece was removed for examination, and the abdomen closed. Microscopic examination showed the tumor to be an adenocarcinoma.

The patient left the hospital on the nineteenth day after operation with his wound healed, but died six months later of metastases.

CASE 4.—Miss F. C., white, aged 53, a dressmaker, entered the hospital on June 5, 1916, because of generalized abdominal pain of four months' duration. For four weeks she had been jaundiced and losing weight. Examination revealed a large mass in the right upper quadrant which moved with respiration and was not tender. A plain plate of the abdomen showed no abnormal shadows. Operation revealed a carcinoma of the gallbladder with metastasis in the liver. Cholecystectomy was done. The section of a piece of the tumor from the gallbladder showed carcinoma with an acute inflammatory reaction.

The patient died on the sixth day after operation.

CASE 5.—Mrs. H. G. W., aged 54, a housewife, entered the hospital on May 29, 1917, because of attacks of pain in the right upper quadrant. At operation, a thickened carcinomatous gallbladder was found adherent to the liver, and containing stones. The lymph nodes along the common duct were involved. The stones were removed and a cholecystostomy done. Microscopic examination of one of the lymph nodes showed carcinoma.

The patient was discharged with the wound healed on the eighteenth day after operation, but died eight months later of generalized metastases.

CASE 6.—Miss G. F., white, aged 53, a nurse, entered the hospital on Nov. 1, 1917, because of an acute attack of pain in the right upper quadrant. The blood count was: hemoglobin, 55 per cent; red blood cells, 3,000,000; white blood cells, 10,000; polymorphonuclear leukocytes, 70, and lymphocytes, 30. At operation, the gallbladder had the appearance of acute cholecystitis. It was removed, and the

common duct explored. No stones were found. The microscopic report was carcinoma of the gallbladder.

The patient died four months after operation of peritoneal and pulmonary metastases.

CASE 7.—Miss N. F., white, aged 52, no occupation, entered the hospital on Jan. 22, 1918. For six months she had had intermittent pain in the right upper quadrant, radiating to the back and associated with gaseous eructations. During this time she had lost 20 pounds (9 Kg.) in weight. For two weeks she had been jaundiced. No tumor could be felt. Operation revealed a thickened gallbladder containing stones. The cystic duct was completely closed, and the mass compressed the hepatic duct. The liver was involved by direct extension. Cholecystectomy was done. Microscopic examination showed carcinoma of the gallbladder with acute inflammation.

Death occurred on the ninth day after operation.

CASE 8.—Mrs. J. R., white, aged 53, a housewife, entered the hospital on April 13, 1918, because of pain in the right upper quadrant, radiating to the back and right shoulder, which had been present for seven weeks. For ten days she had been jaundiced, but the color of the stools had not been noted. The blood count was: hemoglobin, 75 per cent; red blood cells, 5,000,000; white blood cells, 9,000; polymorphonuclear leukocytes, 78, and lymphocytes, 22. The liver was large and nodular, extending 3 inches (7.6 cm.) below the costal margin. At operation, the gallbladder was found to be a mass of carcinoma firmly attached to the liver, which was also extensively involved, as were the lymph nodes along the common and hepatic ducts. Microscopic examination of a lymph node showed alveolar carcinoma.

The patient left the hospital on the eighteenth day, the wound having healed by primary union, but she failed to return for follow-up examination.

CASE 9.—Miss M. C., white, aged 53, no occupation, entered the hospital on July 26, 1919, because of pain in the right upper quadrant with jaundice of several weeks' duration. A general debility had been noticed for several months. The blood count was: hemoglobin, 88 per cent; red blood cells, 4,600,000; leukocytes, 6,600; polymorphonuclear leukocytes, 55, and lymphocytes, 35. The coagulation time was four and one-half minutes. Operation revealed a gallbladder with the gross appearance of carcinoma which was adherent to all adjacent structures. It contained stones, and one was also removed which blocked the common duct. No metastases could be found in the liver or adjacent glands. Cholecystectomy was done. The microscopic diagnosis was medullary carcinoma of the gallbladder with invasion of the attached pieces of liver tissue.

Death occurred on the eighth day after operation.

CASE 10.—Mrs. M. G., white, aged 62, a housewife, entered the hospital on July 13, 1922, because of vomiting. This had been present for three weeks and occurred one hour after each meal. She had lost 18 pounds (8.2 Kg.) in the month before admission. A mass could be felt in the right upper quadrant. Two and one-half quarts of fluid was obtained by gastric lavage. The free hydrochloric acid was 6 and the total acid 30. Roentgenograms of the gastro-intestinal tract showed a deformed duodenal cap and retention in the stomach at twenty-four hours. The blood count was: hemoglobin, 88 per cent; red blood cells, 3,700,000; white blood cells, 8,400; polymorphonuclear leukocytes, 71; lymphocytes, 28, and basophils, 1 per cent. At operation a greatly thickened gallbladder was found with all the adjacent glands involved. Cholecystectomy and excision of one gland was done. The gallbladder contained one stone. Microscopically, the gallbladder and gland showed a mucoid type of carcinoma.

The patient died immediately after operation, and an autopsy showed extensive metastasis to the liver and the glands along the aorta. The ovaries were normal.

CASE 11.—Mrs. M. B., white, aged 54, a housewife, entered the hospital on Sept. 12, 1922, because of epigastric pain which radiated to the right scapula and which had been present for eight days. Jaundice had been noticed with dark urine and clay-colored stools for six days. For some time previously the patient had been losing weight. The blood urea was 12.5 mg., and the blood sugar 105 mg. per hundred cubic centimeters of blood. An orange-sized mass could be felt at the margin of the liver.

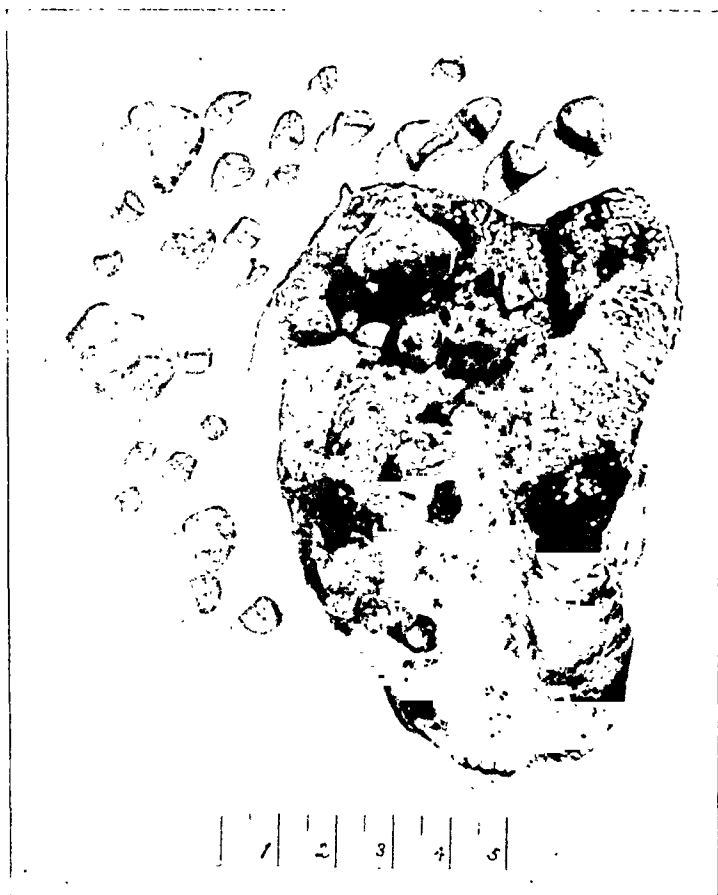


Fig. 1.—Specimen from case 11. The gallbladder is laid open. The carcinoma can be seen at the fundus, involving more than half of the gallbladder. The loose stones came chiefly from the uninvolved portion; the others lie as found.

Operation revealed a large thick gallbladder containing more than sixty stones (fig. 1). The hepatic duct was obstructed by the pressure of metastases in the lymph nodes. Cholecystectomy with drainage of the hepatic and common ducts was done. The microscopic diagnosis was adenocarcinoma of the gallbladder.

The patient was discharged twenty-six days after operation with no drainage and only slight jaundice. When last seen one year after operation, she was fairly well and only slightly jaundiced.

CASE 12.—Mrs. F. M., white, aged 49, a housewife, entered the hospital on Aug. 25, 1923. Five weeks before she had had a sharp severe pain in the right

upper quadrant which radiated to the back and right shoulder. Two days later she became jaundiced. These symptoms persisted to the time of admission. Ten and three months before admission she had had similar attacks. For ten months she had had gaseous eructations, and during this time had lost 25 pounds (11.3 Kg.) in weight.

A plain plate of the abdomen showed nothing abnormal. Roentgenograms of the gastro-intestinal tract showed a spasm of the pylorus which was reported as probably due to gallbladder disease. A test meal gave free hydrochloric acid 54 and total acid 90. The blood count was: hemoglobin, 100 per cent; red blood cells, 5,100,000; white blood cells, 7,400; polymorphonuclear leukocytes, 64, and lymphocytes, 36. The coagulation time was four and one-half minutes.

Operation revealed a carcinomatous gallbladder containing six stones. It appeared to be acutely inflamed. The nodes along the biliary ducts were involved. Cholecystectomy with choledochostomy was done. The diagnosis was confirmed by microscopic examination.

The patient died four hours after operation.

CASE 13.—Mrs. A. D., white, aged 68, a housewife, entered the hospital on June 13, 1924, because of a lump which had been noticed in the right upper quadrant for the preceding five months. With this she had had recurrent attacks of vomiting, pain in the right upper quadrant and constipation. She had lost weight for six months. A mass could be felt in the right upper quadrant. A preoperative specimen of urine showed 1.7 per cent sugar with acetone and diacetic acid. The post-operative specimen contained the same.

At the operation the gallbladder was definitely carcinomatous, but no metastases were noted. It contained twenty-five stones (fig. 2). Cholecystectomy was done. The diagnosis of carcinoma was confirmed by microscopic examination.

The patient died one day after operation in diabetic coma.

CASE 14.—Mr. H. S., white, aged 62, a barber, entered the hospital on March 1, 1925, because of intermittent attacks of pain in the right upper quadrant which radiated to the back. From the age of 17 to 35 he had had attacks of the same pain associated with chills, fever, vomiting and jaundice. A small rounded mass could be felt in the right upper quadrant. The laboratory findings were: hemoglobin, 92 per cent; red blood cells, 4,600,000; urea, 14.3 mg. per hundred cubic centimeters of blood, and phenolsulphonphthalein output, 52 per cent.

The operative findings were those of cholecystitis and cholelithiasis. Cholecystectomy was done. Examination in the laboratory revealed a small carcinoma in the fundus. This was verified by microscopic examination.

The patient made an uneventful recovery, and at the present time is alive and free from symptoms, more than six years later.

CASE 15.—Miss S. S., white, aged 48, a painter, entered the hospital on Feb. 27, 1925, complaining of epigastric pain in the right upper quadrant which radiated to the back and right shoulder. This had been present for three months. Jaundice, clay-colored stools and nausea, but no vomiting, had been present for six weeks. The bile index was 143, and the urine contained much bile. Exploratory laparotomy revealed a shrunken distorted gallbladder and carcinomatous nodules in the liver. Biopsy showed mucoid carcinoma. There was no ascites.

Following operation, the patient became apathetic, gradually failed, went into collapse and died six days after operation.

CASE 16.—Mrs. F. G., white, aged 55, a housewife, entered the hospital on Oct. 24, 1927, because of pain in the right upper quadrant radiating to the back and

right shoulder, associated with vomiting and gaseous eructations. She had been having such attacks for nineteen years. No masses could be felt. The blood count was: hemoglobin, 86 per cent; red blood cells, 4,600,000; white blood cells, 6,800; polymorphonuclear leukocytes, 64, and lymphocytes, 36. The blood urea was 10 mg. and the uric acid, 4.2 mg. per hundred cubic centimeters of blood. The phenol-sulphonphthalein output was 50 per cent.

The operative diagnosis was cholecystitis and cholelithiasis. Cholecystectomy was done. When the gallbladder was opened, a papillary adenocarcinoma and one stone were found. This diagnosis was confirmed microscopically.

The patient was discharged with the wound completely healed on the seventeenth day after operation and died twenty-one months later of metastases in the liver.

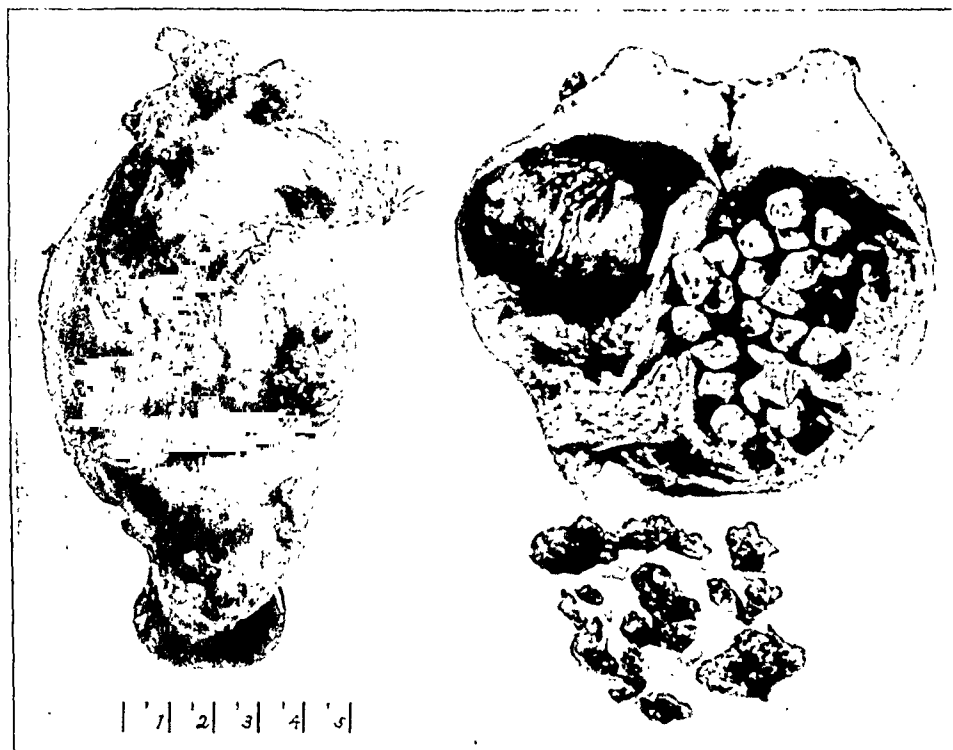


Fig. 2.—Specimen from case 13. Tarry bile can be seen oozing from the cut cystic duct of the unopened specimen. The nodular appearing protuberance is the carcinoma at the fundus, a cross-section of which is seen in the opened specimen. The irregular objects outside of the gallbladder are partly necrotic portions of the papillary outgrowth from the cancer which broke off when the specimen was opened.

CASE 17.—Mr. J. B., white, aged 61, a manufacturer, entered the hospital on May 28, 1929. For the preceding six weeks he had recurrent attacks of acute pain in the right upper quadrant radiating to the right shoulder. With this there were usually vomiting and jaundice. One year before he had a similar attack without jaundice. There was a palpable mass in the gallbladder region. The blood count was: hemoglobin, 93 per cent; red blood cells, 4,600,000; white blood cells, 11,800; polymorphonuclear leukocytes, 72, and lymphocytes, 28.

At operation, a hard indurated mass filled the gallbladder region. It was opened, and three stones were found and removed. The tissue about them appeared necrotic. Cholecystostomy was done. All adjacent structures were extensively involved by

direct extension of the carcinoma. The diagnosis was confirmed by microscopic examination.

The patient died three days after operation.

CASE 18.—Mrs. L. K., white, aged 65, a housewife, entered the hospital on Sept. 8, 1929, because of jaundice and loss of 15 pounds (6.8 Kg.) in weight in the four weeks preceding. She had had recurrent attacks of severe pain in the right upper quadrant for fifteen years. No mass was felt. The blood urea was 19.2 mg. per hundred cubic centimeters of blood. The bile index was 50. The coagulation time was five minutes and the bleeding time three minutes.

At operation, a thickened friable gallbladder was found which contained stones. It tore off while being removed. The common and hepatic ducts were explored but no stones found. Microscopic examination showed carcinoma of the gallbladder wall.

Death occurred nine days after operation.

CASE 19.—Mr. L. M., white, aged 70, no occupation, entered the hospital on Aug. 12, 1930. He had been coming in at intervals over a period of eighteen years for treatment for an old cerebrospinal syphilis. At various times he had complained of indigestion and pain in the right upper quadrant. Two roentgenographic series of the gastro-intestinal tract made four and five years before admission were reported normal.

On entrance to the hospital, the patient complained of a severe pain associated with nausea and vomiting of two weeks' duration. The bile index was 13. The blood count was: hemoglobin, 88 per cent; red blood cells, 4,000,000; white blood cells, 8,400; polymorphonuclear leukocytes, 88, and lymphocytes, 12. A mass could be palpated in the right upper quadrant which was very tender. This disappeared in about ten days, and the pain disappeared at the same time. With the recurrence of pain, the mass reappeared. The patient had a septic temperature, ranging from 101 to 105 F.

The first cholecystogram showed faint filling; a second showed none. Roentgenograms of the gastro-intestinal tract revealed a constant deformity of the first and second parts of the duodenum, attributed to adhesions. A clysm indicated adhesions about the hepatic flexure.

Operation revealed a large gallbladder adherent to all adjacent structures. It was white and filled with a gelatinous material in which were several stones. The liver, adjacent glands and peritoneum contained many metastases. The peritoneal cavity contained a small amount of serosanguineous fluid. A culture from the gallbladder grew *Bacillus coli*. Microscopic examination confirmed the diagnosis of carcinoma.

The patient died of generalized metastases six months after operation.

NOTE: These patients were operated on by the various members of the surgical staff of St. Luke's Hospital and the case reports are presented here with their permission. Case 19 is the only case in which operation was performed personally by the authors.

Only those cases in which the carcinoma was found at operation and the diagnosis confirmed by microscopic examination are included in this list which covers the period from 1916 to 1930, inclusive. Eleven other cases of carcinoma of the gallbladder were found at operation before 1916 at St. Luke's Hospital, but their records were too incomplete to be included in this present report. Their diagnoses were all confirmed by microscopic examination, however.

The comprehensive discussion of the subject by Rolleston and McNee in their book has been of the utmost value in the preparation of this paper.



# ENDOTHELIOMA OF THE DURA (MENINGIOMA)

REPORT OF AN UNUSUAL CASE

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AND

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The term endothelioma of the dura has been more or less successfully retained in the literature in spite of the fact that the true origin of these tumors is probably from the leptomeninges. Schmidt,<sup>1</sup> Weed<sup>2</sup> and Cushing and Weed<sup>3</sup> called attention to frequent calcareous deposits in the arachnoid membrane of man and adult lower mammals and their association with nests of cells due to hyperplasia of the arachnoid mesothelium. They emphasized that the so-called dural endotheliomas show histologically the same cellular arrangement as these nests of cells, and that hence they probably take their origin from the arachnoid mesothelium. Cushing preferred to refer to them as meningiomas. Mallory<sup>4</sup> discussed in detail the structure of these tumors and followed the authors named in ascribing their origin to the fibroblasts of the arachnoid villi. He suggested the term arachnoid fibroblastoma for these tumors, and considered them closely related to the tumors developed from the perineurium of the peripheral nerves, which he designated as perineurial fibroblastoma. Van Wagenen<sup>5</sup> and Penfield<sup>6</sup> followed Mallory in this usage. We have retained the term endothelioma of the dura on account of the physical relationship of these tumors to the dura and to conform to ordinary clinical usage in referring to these tumors.

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From the Neurological and Surgical Service of the Cook County Hospital.

1. Schmidt, M.: Ueber die pachionischen Granulationen und ihr Verhaeltnis zu den Sarkomen und Psammomen der Dura mater, Virchows Arch. f. path. Anat. **170**:426, 1903.

2. Weed, L. H.: The Cells of the Arachnoid, Bull. Johns Hopkins Hosp. **31**:343, 1920.

3. Cushing, H., and Weed, L. H.: Studies on the Cerebrospinal Fluid and Its Pathway: IX. Calcareous and Osseous Deposits in the Arachnoidea, Bull. Johns Hopkins Hosp. **26**:367, 1915.

4. Mallory, F. B.: The Type Cell of the So-Called Dural Endothelioma, J. M. Research **41**:349, 1920.

5. Van Wagenen, W. P.: Elastic Tissue in Meningeal Fibroblastoma, So-Called "Dural Endotheliomas," Arch. Surg. **18**:1621 (April) 1929.

6. Penfield, W. G.: Cranial and Intracranial Endotheliomata-Hemicranosis, Surg., Gynec. & Obst. **26**:657, 1923.

They are of fairly frequent occurrence. Cushing,<sup>7</sup> in a series of 748 verified cases of brain tumor, reported 80 cases (10.7 per cent) of dural endotheliomas.

The relationship of these tumors to the skull is of interest. Cushing, in the aforementioned report, stated that twenty of his cases of dural endothelioma (25 per cent) were accompanied by a recognizable thickening of the overlying bone. He stated that the flat endotheliomas are more likely to provoke bony proliferation. According to him, the invasion of the bone canaliculi by tumor cells stimulates osteoblastic proliferation and subsequent hyperostosis. He also spoke of cases in which the bone is thinned or eroded, but gave no data as to the frequency of these cases.

Penfield<sup>6</sup> reported eleven cases from the literature and ten from his own studies, in all of which the patient gave a history of a gradually increasing lump over the cranial vault. In four of the cases from the literature microscopic examination showed actual infiltration of the bone by the tumor. From his own observations Penfield concluded that these tumors rarely or never penetrate the pia, and that they do infiltrate the overlying skull and scalp with bony proliferation. He stated that there is first rarefaction of the overlying bone and then stimulation of new bone formation. Endothelioma cells fill up the haversian systems, and there is a pad of endothelioma at the apex of the tumor just beneath the scalp. At this point the greatest osteogenic activity is found.

Phemister<sup>8</sup> reported three cases, two with localized hyperostosis and one with localized bone erosion and a little associated new bone formation. Barling and Leith<sup>9</sup> reported a case of a tumor arising in the pia-arachnoid and penetrating the dura to invade the overlying bone. There was marked osteoporosis but no attempt at new bone formation. The pathologic report was sarcoma of the endotheliomatous type, but the description and figures were those of a typical dural endothelioma.

Kolodny<sup>10</sup> studied ten cases of dural endothelioma, all with attached bony thickening. He explained the bony proliferation on the basis of local dilatation of the vascular channels of the skull, in turn due to growth of the underlying tumor mass, causing their stasis. Later invasion of the bone by tumor cells leads to bone destruction and

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7. Cushing, H.: The Cranial Hyperostoses Produced by Meningeal Endotheliomas, *Arch. Neurol. & Psychiat.* 8:139 (Aug.) 1922.

8. Phemister, D. B.: The Nature of Cranial Hyperostosis Overlying Endothelioma of the Meninges, *Arch. Surg.* 6:554 (March) 1923.

9. Barling, H. G., and Leith, R. F. C.: Removal of a Cerebral Tumor (Endothelioma) Which Had Invaded the Overlying Cranial Bone, *Lancet* 2:282, 1906.

10. Kolodny, A.: Cranial Changes Associated with Meningioma: "Dural Endothelioma," *Surg., Gynec. & Obst.* 48:231, 1929.

occasionally to complete perforation of the skull. Taylor<sup>11</sup> reported a case in which the tumor was attached to the dura and had eroded the bone above it.

Thus, out of thirty-six cases (excluding Cushing's series) we have been able to find definite mention of only three cases in which there was definite destruction of the overlying bone.

The dural endotheliomas have usually been considered as benign tumors on the basis of the usual criteria. However, Taylor<sup>12</sup> cited from the literature two cases of dural tumor with metastases and three cases with invasion of the brain. The latter is unusual, as Hassin<sup>13</sup> and Hassin and Singer<sup>14</sup> have shown that in carcinoma of the cerebral meninges there is no invasion of brain tissue unless (as in one case that they reported) the subarachnoid space is so packed with tumor cells that the pressure forces them into the cerebral adventitial spaces. Even in such case only the superficial layers of the cerebral tissue are involved. Taylor considered the dural tumors as of low grade malignant character and characterized by slow spread, local malignancy and occasional metastases. Craig<sup>15</sup> presented a series of fifty-six cases of intracranial endotheliomas, eleven of which he considered malignant on the basis of absence of psammoma bodies, slight differentiation of cells and the presence of many mitotic figures. On the qualitative differences in the last two points he established a system of grading the malignancy.

We are presenting a case of intracranial tumor of long duration, originating from the dura, eroding the bone without any evidence of bony proliferation and bearing close microscopic resemblance to a malignant tumor.

#### REPORT OF A CASE

W. K., a man, 54 years of age, Polish, was admitted to the neurologic service (Dr. G. B. Hassin) of the Cook County Hospital on Jan. 31, 1930. He complained of numbness of the right extremities of three months' duration, weakness of the right extremities of one month's duration, a sensation of fulness in the head for two weeks, and an epileptiform attack on one occasion two days previous to admission.

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11. Taylor, W. J.: Report of a Case of Tumor of the Brain; Operation; Recovery; Death in 108 Days from Recurrence of the Disease, *Am. J. M. Sc.* **127**:287, 1904.

12. Taylor, J.: Invasion of the Skull by Dural Tumors, *Brit. J. Surg.* **16**:6, 1928.

13. Hassin, G. B.: Histopathology of Carcinoma of the Cerebral Meninges, *Arch. Neurol. & Psychiat.* **1**:705 (June) 1919.

14. Hassin, G. B., and Singer, H. D.: Histopathology of Cerebral Carcinoma, *Arch. Neurol. & Psychiat.* **8**:155 (Aug.) 1922.

15. Craig, W. M.: Malignant Intracranial Endothelioma, *Surg., Gynec. & Obst.* **45**:760, 1927.

He stated that he had been perfectly well until three months previously when, while at work, he was walking through a low door and, straightening up too soon, struck the vertex of his head severely against the top of the door. He did not fall or become unconscious at that time or later. There was no bleeding at any of the orifices nor was there any laceration of the scalp. A swelling in the left frontoparietal region was noted by the examiner and ascribed by the patient to a childhood injury thirty-five years previously. He stated that it had remained constant in size and had given no symptoms during all that time. Since his injury, three months previously, he stated that his right arm and leg felt numb, as though they were "asleep." Weakness of the right extremities had been present for one month and was more marked in the lower one. At the time of admission the patient felt that his right arm was improving. For two weeks a feeling of pressure, described as a "sensation of fullness," had been present intermittently in the left frontal region. Two days before admission the patient was sleeping at night and awoke at 1 a. m. About an hour later he had a convulsive attack consisting of "jerking" movements of the right arm and leg that lasted for about one minute. There was no aura, he did not cry out or lose consciousness, nor did he have bladder or rectal incontinence. He could not recall whether the attack began in the arm or in the leg. A similar attack of like duration occurred an hour later and he had had none since.

The patient was a laborer who had come to this country in 1914. He admitted the occasional use of alcohol, but stated that he had not used it for the past two months. His wife had had six children and no miscarriages, and he denied syphilitic infection. His past history and the family history were otherwise essentially unimportant.

General physical examination at the time of his admission revealed a well nourished, well developed, white man, about 50 years of age, who was not acutely ill. The temperature, pulse rate and respiration rate were normal, and the blood pressure was 138 systolic and 65 diastolic. There was a swelling in the left frontoparietal region, just to the left of the midline. This swelling was about the size of an English walnut, firm, nonfluctuant, firmly fixed to the skull and slightly tender. Pressure applied to the swelling caused no symptoms or subjective sensations. All the teeth were missing except the lower premolars and they were carious. There was a direct, reducible, incomplete, right inguinal hernia. The right testicle was atrophied, and there was a telangiectatic hemangioma on the dorsum of the left hand.

Neurologic examination revealed a slight spasticity of the gait, with a tendency to circumduction of the right lower extremity. The right arm was held motionless as the patient walked. The coordination tests were all satisfactorily performed with the exception of the finger to finger and right finger to nose tests which were done poorly. Muscle power was good in all the extremities and apparently equal. There was a slight increase in muscle tonus in the right lower extremity. The deep reflexes were moderately increased in the right lower extremity, and there was a sustained ankle clonus on the right side. The superficial reflexes were all present and equal, and there were no pathologic reflexes. All types of sensibility appeared to be normal, and there were no abnormalities of the cranial nerves. Examination of the fundi gave negative results.

The Kahn reaction of the blood was negative, the chemical composition of the blood essentially normal and the results of urinalysis essentially negative. Spinal puncture failed and the patient refused cisternal puncture. Roentgen examination of the skull revealed a defect near the midline, halfway between the lambdoid and coronal sutures. This defect was circular in outline and well defined, and there

was no evidence of associated bony proliferation. Unfortunate loss of the negatives prevents their reproduction. Roentgen examination of the long bones revealed no pathologic changes.

Dr. Hassin examined the patient and considered the condition to be associated probably with the tumor of the left frontoparietal region. He considered this tumor to be most likely an endothelioma in spite of the history of long duration with no symptoms before three months previously. He recommended operation, and the patient was transferred to a surgical service (Dr. George G. Davis) on February 20. His status had remained unchanged while he was on the neurologic service.

One of us (Dr. Davis) operated on the patient on March 10. A tumor mass, well defined, about the size of a plum and firm in consistency, was found adherent to the dura and extending through the eroded area of the skull. This tumor was

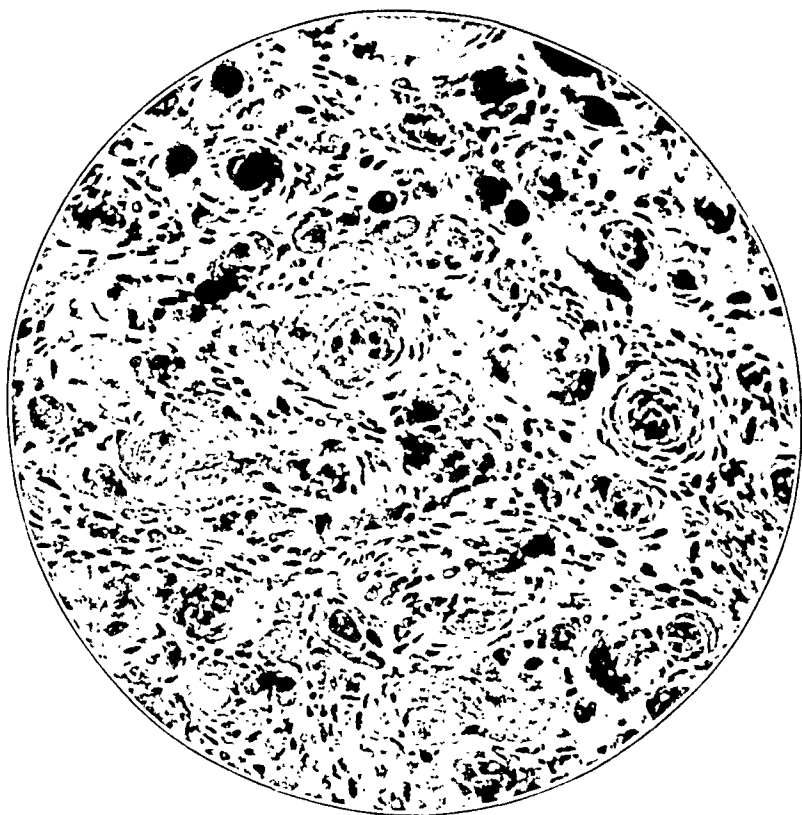


Fig. 1.—Dural endothelioma containing numerous whorls formed around hyaline masses of collagen fibrils. (Reproduced from Mallory: Principles of Pathological Histology.)

removed and sent to the pathologic laboratory for histologic examination. The report of the laboratory was that it was a squamous cell carcinoma, apparently metastatic.

The patient made an uneventful recovery from the operation. Thirteen days after the operation, neurologic examination revealed a definite weakness of both right extremities, a typical hemiplegic gait and a right foot drop. The deep reflexes were increased on the right side; there was a sustained ankle clonus on the right side, with a positive Babinski sign. The patient was transferred back to the neurologic service on March 23.

The laboratory report on the tissue removed led to further questioning of the patient and careful reexamination, neither of which yielded any clue as to the possible presence or location of a primary carcinoma. The patient's condition failed to improve, and he occasionally had an epileptiform seizure involving the right extremities. He was transferred to the county infirmary on June 4. He left this institution on August 14, in approximately the same condition as on admission, still alive, in good general health and with his hemiplegia slightly improved.



Fig. 2.—Photomicrograph showing avascular cell masses in a stroma of hyaline connective tissue;  $\times 80$ .

The history of long duration of this tumor, the failure to discover any primary carcinomatous focus and the fact that the patient continued to remain in good physical condition all spoke against the original histologic diagnosis of the tumor. Hence one of us (Dr. Voris) reexamined the microscopic sections under the direction of Dr. Hassin with the aid of additional sections stained by the van Gieson technic. In addition Dr. Hassin has loaned us a section of carcinoma of the dura, a

photomicrograph of which we here reproduce (fig. 4) together with photomicrographs of our own (figs. 2 and 3).

The latter sections were stained both with hematoxylin and eosin (fig. 2) and also by the van Gieson method (fig. 3). They contained many avascular masses of deeply staining epithelial cells. In the van Gieson preparations these cell masses often contained pink staining

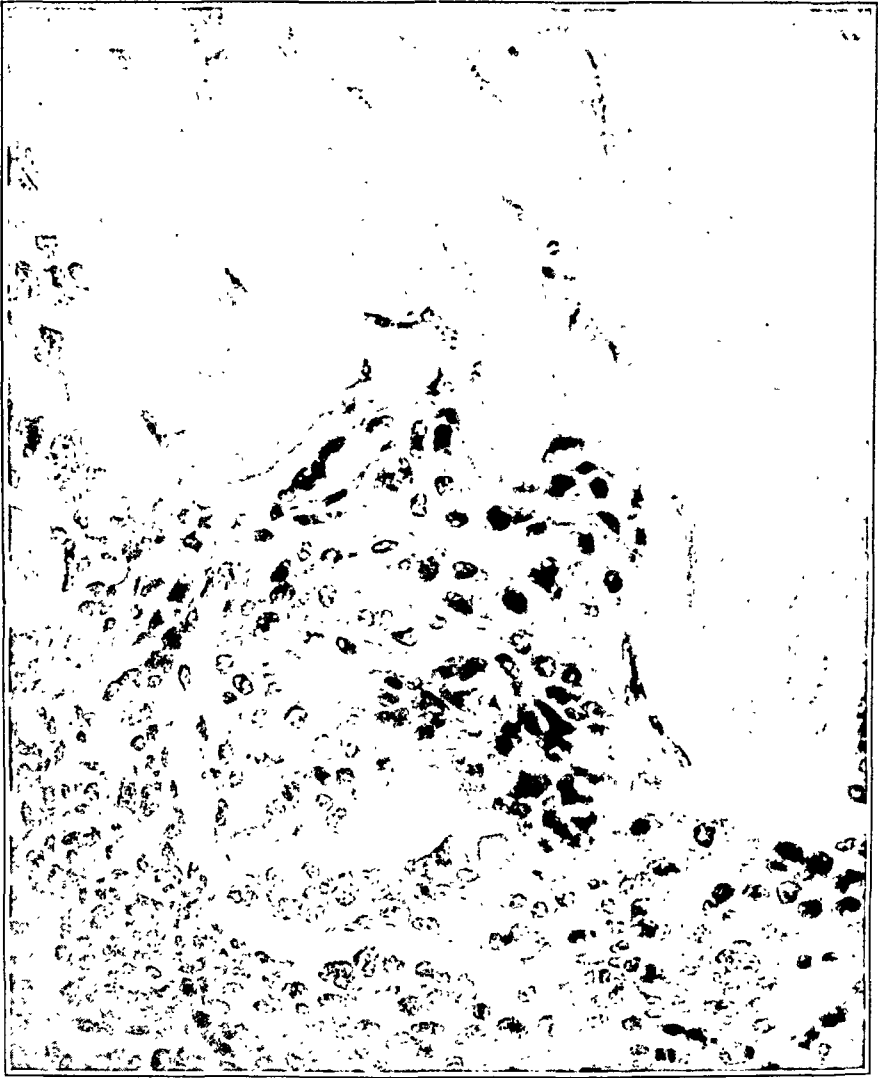


Fig. 3.—Same tissue as in figure 2;  $\times 275$ .

fibers made up of many fine fibrils. At times these cell masses presented well defined borders, and at times the cells were arranged more or less in the form of whorls. There was no limiting membrane around the cell masses, and the cells often extended diffusely into the surrounding tissue and at times infiltrated it. In many of their nuclei there was a small dark nucleolus. No mitotic figures could be made out although the chromatin granules were excellently stained. In the center of

the larger cell masses many of the nuclei were shrunken, irregular, very deeply stained and occasionally even fragmented.

These cell masses were located in a stroma of pink staining, homogeneous, hyaline fibers which appeared slightly granular in the hematoxylin and eosin preparations and showed marked fibrillar structure in the van Gieson preparations. Many fibroblasts were scattered among



Fig. 4.—Photomicrograph of a metastatic carcinoma of the dura invading the underlying brain tissue: *A*, dura; *B*, leptomeninges and subarachnoid space, and *C*, brain;  $\times 80$ .

these fibers, and in certain areas there were the infiltrating strands of the epithelial cells mentioned. In certain areas the fibers were much shrunken, sometimes fragmented, or even broken into small granules. These areas were much more lightly stained. The fibroblasts in these areas had their cytoplasm shrunken or entirely absent, and the nuclei were also shrunken, irregular in outline, deeply stained and, at times,



fragmented. In and around these areas blood cells were frequently present in small masses free in the interstices between the fibers. Blood vessels were generally absent from these areas and were few in number everywhere. Many of the blood vessels had their walls greatly thickened, and at times the lumen was almost occluded. These thickened walls presented a uniform homogeneous pink staining appearance.

For comparison with our material we are reproducing (fig. 1) a drawing of a typical dural endothelioma taken from Mallory's *Principles of Pathological Histology*.<sup>16</sup> This illustrates well the tendency of the typical dural endothelioma to form whorls of cells around hyaline masses of collagen fibers.

In figure 4 we present a photomicrograph of an unquestionable metastatic carcinoma of the cerebral meninges which was loaned to us by Dr. Hassin. The upper part of the picture represents the meninges infiltrated with numerous foci of carcinomatous cells; the lower part is the brain. Some vessels here show perivascular infiltrations with carcinomatous cells. The dura occupies the uppermost part of the picture. Attention should be called to the lack of reaction on the part of the connective tissue stroma, to the foci of small deeply staining cells and to the tendency of the latter cells to extend into the perivascular spaces of the underlying cerebral blood vessels. But this last occurs only when, as in this case, the subarachnoid space is very densely infiltrated with carcinoma cells. The gross appearance of this tumor is strikingly different from that of our tumor. It presents the appearance of multiple plaques infiltrating the dura overlying the brain. On the other hand, our tumor was a circumscribed mass definitely attached to the dura but not infiltrating it.

#### COMMENT

The following possibilities are present in this case. It may be, as first reported, a squamous cell metastatic carcinoma; it may be a dural endothelioma or meningioma, or finally, it may be a dural endothelioma of malignant character. Against the first possibility, that of a metastatic carcinoma, are the failure to discover a primary carcinomatous focus, the history of long duration before symptoms set in, the final slow onset, the single lesion, the failure to discover mitotic figures, the lack of symptoms of increased intracranial pressure and the present good general condition of the patient. Globus and Salinsky<sup>17</sup> reported twelve cases of metastatic tumor of the brain and stated that they were characterized by acute or precipitate onset, symptoms of increased intra-

16. Mallory, F. B.: *Principles of Pathological Histology*, Philadelphia, W. B. Saunders Company, 1914

17. Globus, J. H., and Salinsky, H.: Metastatic Tumors of the Brain, *Arch. Neurol. & Psychiat.* **17**:481 (April) 1927.

cranial pressure out of proportion to the neurologic observations, occasional signs of meningeal irritation, occasional pleocytosis and a rapidly declining clinical course.

The tendency of the epithelial cells to infiltrate the surrounding stroma in certain areas might speak for a low grade malignancy. Against this are the extremely slow growth of the tumor, the absence of mitotic figures and the absence of metastases.

The general structure of the tumor, the minute features already mentioned, the clinical course and the present good condition of the patient all point, it seems to us, to the diagnosis of endothelioma of the dura.

#### SUMMARY

A case of endothelioma (meningioma) of the dura is presented. The tumor was of thirty-five years' duration with symptoms only during the three months previous to the patient's admission to the hospital. It had eroded the skull, with no attempt at new bone formation. Pressure on the tumor gave no symptoms or subjective sensations. Operative removal aggravated the symptoms with gradual improvement and a residual hemiplegia. Microscopically, the structure of the tumor was that of an atypical endothelioma of the dura with slight evidence of low grade malignancy.

# HISTOLOGY OF HEALING FRACTURES IN RATS ON NORMAL DIETS

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Our understanding of the problems of bone development and growth draws on many fields of scientific endeavor in order to build up a complete philosophy of the subject. A purely anatomic and histologic approach, while extremely valuable and for many years our only method of attacking the subject, gave us but a very incomplete picture of the natural history of bone. Tissue cultures, when added to the already existing data furnished by ground and decalcified sections, carried forward our appreciation of this complex subject.

Now, more recently, we have been enabled to add to our previous information that gained by studies on the physical structure and chemical composition of bone, and are well on the way to a more comprehensive understanding of osseous tissue than we possessed before. On the basis of our newer knowledge, it becomes necessary to revise somewhat the older views of bone physiology and pathology.

In a rather comprehensive series of studies on the breaking strength of healing fractured fibulae in rats on various synthetic diets reported by Lindsay and Howes<sup>1</sup> and later by McKeown, Lindsay, Harvey and Lumsden,<sup>2</sup> it was decided to study the histology of the changes involved in the healing of these fractured bones. It was felt that a correlation between the observed callus strength and the histologic picture could be obtained and that from this the special cell types responsible for the differences in strength from time period to time period throughout the course of the experiment could be determined.

To control future results on unbalanced diets, the animals were first placed on a standard or normal diet for one week and the right

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From the Department of Pathology and Department of Surgery, Yale Medical School.

The expenses of this investigation were defrayed in part by Davis & Geck, Inc.

1. Lindsay, M. K., and Howes, Edward: The Breaking Strength of Healing Fractures, I., *J. Bone & Joint Surg.* **13**:491 (July) 1931.

2. McKeown, R. M.; Lindsay, M. K.; Harvey, S. C., and Lumsden, R.: The Breaking Strength of Fractured Fibulae of Rats: II. Observations on a Standard Diet, *Arch. Surg.* **24**:458 (March) 1932; other papers in this series will follow in succeeding issues of the ARCHIVES OF SURGERY.

fibula was then fractured in the manner described by the aforementioned authors.<sup>3</sup> Two of the normal diet animals with fractured right fibulae were killed on each of the following postoperative time periods: six, twelve, eighteen and twenty-four hours. Two animals were also killed one, two, three, four, five and six days after operation, and at three day intervals thereafter.

The legs were then removed, and the tibiae and fibulae cleaned of all adhering soft tissues. These bones were fixed at once in 10 per cent formaldehyde, washed and embedded in celloidin, and that portion of the fibula containing the fracture was then sectioned longitudinally, and stained with hematoxylin and eosin, Mallory's connective tissue stain or Masson's triple stain. By sectioning the diaphysis longitudinally, a complete picture of the fracture at different levels was obtained.

Professor Maximow expressed his views on the subject of connective tissue growth through his "unitarian" theory.<sup>4</sup> This teaches us that in addition to connective tissue cells arising from the primary mesenchymal cells of the embryo, there is the greatest plasticity in the interchange of these cell types, occurring later in their life cycle. Fibroblasts may differentiate under proper conditions into chondroblasts or chondrocytes, into fat cells or the cells of the elastic tissues and, of particular interest for our purpose at present, into osteoblasts, osteocytes and probably these in turn into the so-called osteoclasts. Further than this, under proper conditions cells of the lymphocytic series, always present in the tissues, may revert to fibroblasts and hence on up to mature and further differentiated types of connective tissue cells.

It is through such studies as those of Maximow and of Häggqvist<sup>5</sup> that our knowledge of fundamental biologic processes has been built up. Häggqvist has had the courage to question the older views, and the energy to demonstrate that the conception of the osteoblasts having some peculiar quality that enables them, like glandular structures, to lay down calcium salts is probably not correct. He further believes that the osteoclasts are not in themselves responsible for the destruction of bone. He demonstrated that the osteoblasts are but the lineal descendants and successors of a rather long chain of connective tissue development, beginning, as Maximow also believed, with the mesenchymal cells, becoming next the fibroblasts and then, depending on whether the particular bone is to be membranous or endochondral,

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3. Lindsay and Howes (footnote 1). McKeown, Lindsay, Harvey and Lumsden (footnote 2).

4. Maximow, A., and Bloom, W.: *A Textbook of Histology*, Philadelphia, W. B. Saunders Company, 1930, pp. 48, 72 and 162.

5. Häggqvist, Gösta: *Acta chir. Scandinav.* **65**:180, 1929.

going directly into osteoblasts or, on the other hand, into chondroblasts, hence to chondrocytes and in turn to osteoblasts. As bone develops, these same cells become the osteocytes or the vital centers of the living, plastic bone. The osteoclasts, he considers, are but a residuum of protoplasm containing the clumped nuclei of osteocytes after the bone has been decalcified by purely chemical changes.

While these views are not accepted by all investigators without question, a careful study of our own material, in which a complete series of histologic preparations of the various stages of bone regeneration may be seen, tends to convince one that these theories, in at least their fundamentals, are correct and acceptable.

### HISTOLOGY

Immediately after fracture of the fibula, blood is poured out from the ruptured vessels both in the bone and immediately adjacent to it to form a blood clot surrounding the line of fracture and extending out into the surrounding soft tissues for a short distance. Within eighteen hours, this has changed into a largely fibrinous clot with many lymphocytes present, but only the shadows of the erythrocytes. At the forty-eight hour period, this clot has become a well defined and outlined callus, made up entirely of fibrin and lymphocytes, and fairly well uniting the two fractured ends within the body of the callus. At this stage, the periosteum and endosteum have become "swollen" appearing and the individual cells may be made out with ease.

On the third day the periosteal and endosteal cells have begun to proliferate, and the lymphocytes within the clot are beginning to be replaced by young fibroblasts, apparently by metaplasia of these cells.

On the fourth day the callus has become entirely fibroblastic connective tissue—continuous with periosteum and the endosteum—completely filling the marrow cavity for some distance in each direction from the fracture line, and showing some tendency toward distinct condensation just across the line of fracture. An occasional large multinucleated cell may be seen along the margins of the still partly calcified trabeculae within the bone marrow and near the cortex. These are the cells commonly spoken of as osteoclasts.

On the fifth day there is further condensation of the fibrous callus through the line of fracture. There is a beginning of proliferation of small vessels and capillaries, and around these capillary buds may be seen irregularly deposited calcium salts. Also at this period many of the fibroblasts out in the body of the callus begin to have a rounded, "swollen" appearance. These are young chondroblasts. This is especially notable near the periphery of the line of fracture. The nuclei



Fig. 1.—Fifth day: fibrous callus, showing fragments of bone being cast off from fractured end. Hematoxylin and eosin;  $\times 80$ .

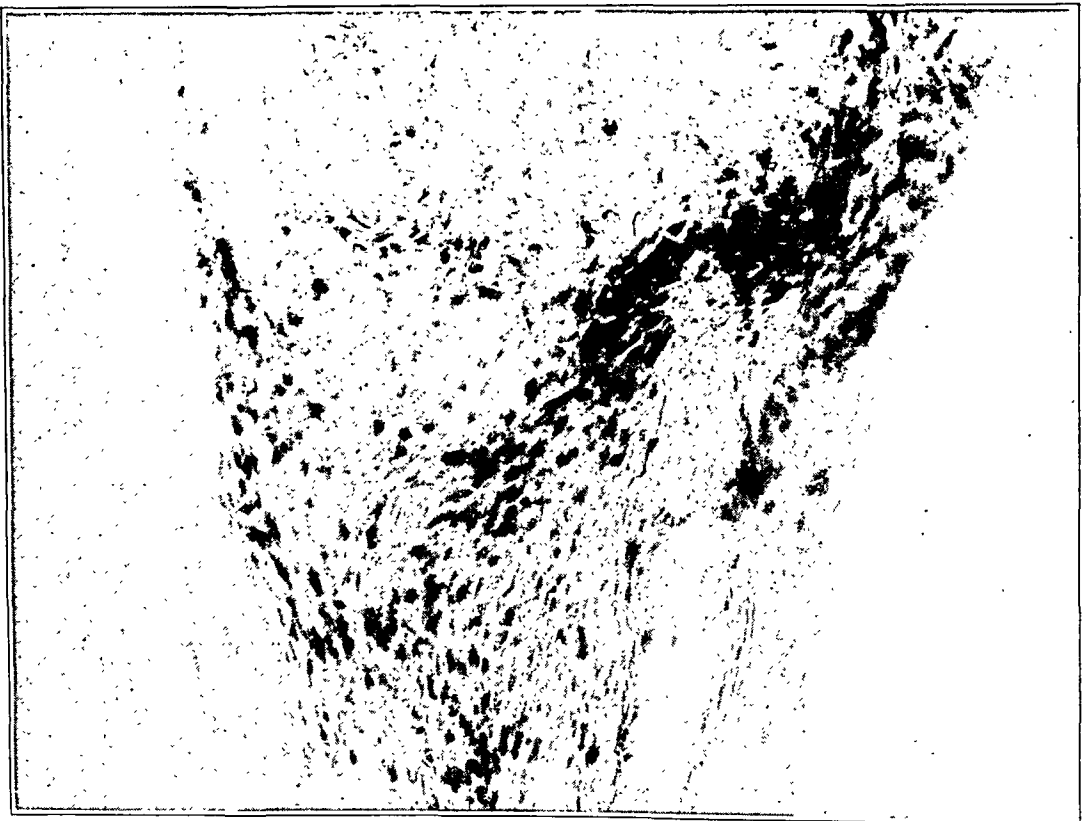


Fig. 2.—Fifth day: fibrous callus in region of proliferating periosteum, showing the "swollen" rounded appearance of the older of these cells. Hematoxylin and eosin;  $\times 300$ .

of the osteocytes in the cortex and trabeculae begin, at this stage, to have a hyperchromatic appearance, and one may begin to see fragmentation of the bone near the fractured end (figs. 1 and 2).

On the sixth day the condensation of the fibroblasts directly in the fracture line and at the periphery, continuous with the periosteum, is more apparent. The large swollen cells near the periphery have begun to show hyperchromatic nuclei and have the appearance of cartilage cells. The infiltration of salts is more obvious and the calcifying areas are more extensive. A greater number of smaller fragments of bone

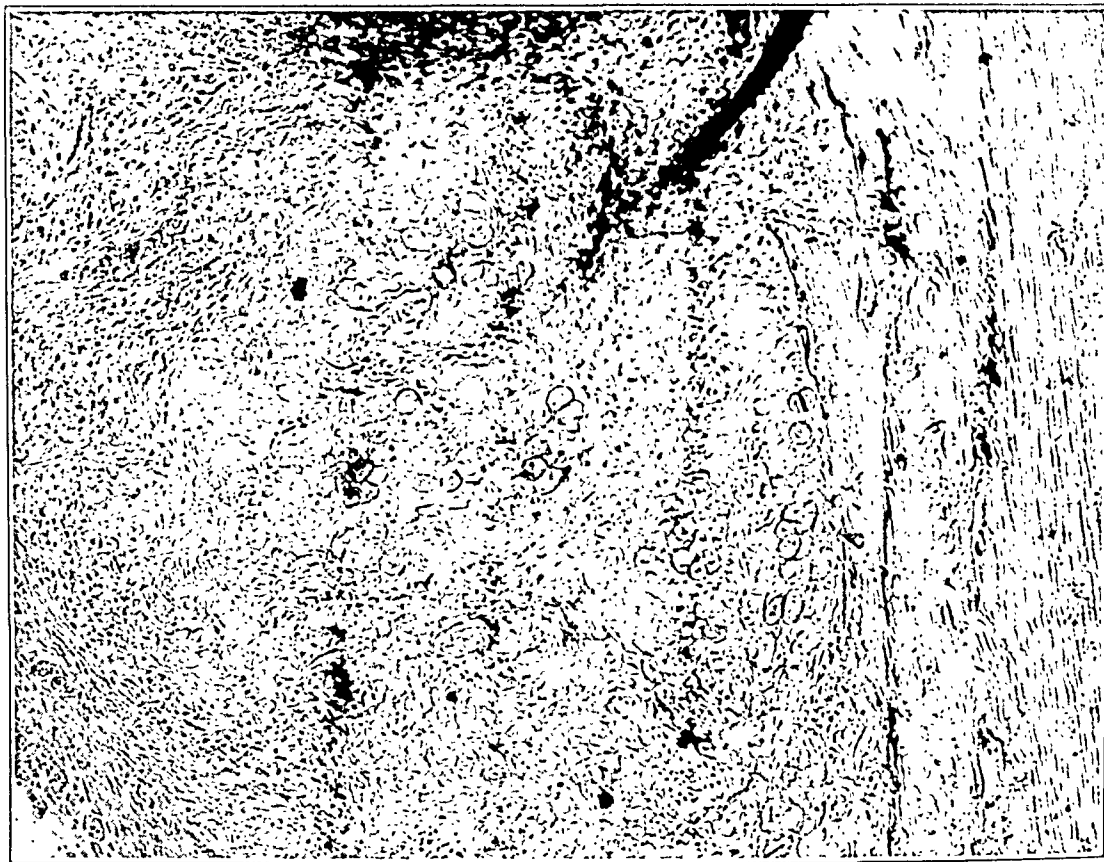


Fig. 3.—Sixth day: large clumps of swollen, rounded fibroblasts or chondroblasts. Many are now definitely seen to be chondrocytes. Hematoxylin and eosin;  $\times 125$ .

may be seen, and the callus is much more highly vascular. More of the fibroblasts have the swollen appearance, while those at the center of such clumps have definitely taken on the characteristics of chondrocytes, and a few are definitely larger and hypertrophic (fig. 3).

On the ninth day the entire callus has become quite vascular, and the deposition of calcium salts forms an irregular network surrounding the capillaries. The masses of cartilage cells have become quite extensive, forming a plate through the line of fracture with a quite thick

mass or ring just inside the periphery of the callus. Many transitional stages between fibroblasts and chondrocytes may be seen at the periphery of this mass, and large clumps of hypertrophic chondrocytes are present. Only very rare bone fragments may now be detected and the cortex is receding from the line of fracture. Clumped around these ends are numerous large multinucleated cells (osteoclasts) (fig. 4).

On the twelfth day there is well marked organization of the callus. The mass of cartilage is larger, the calcifying network is more clearly

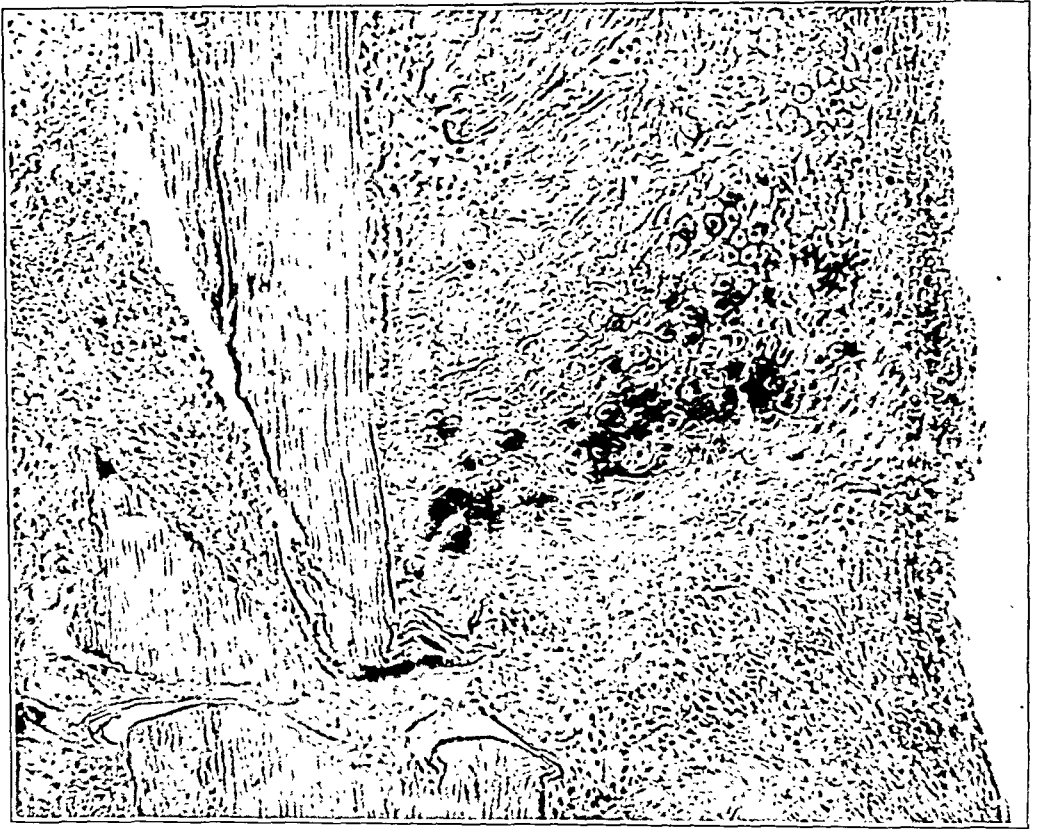


Fig. 4.—Ninth day: clump of chondrocytes; those at the center are becoming hyperplastic. In the upper part of the illustration the vascularity and depositions of calcium may be seen.

defined, and outside of the cartilaginous zone the vascular network is quite complete. There is, however, still no regularity in the pattern formed by any of these elements, nor are they joined across the line of fracture.

On the fifteenth day the calcifying strands have increased in size and density. The trabeculae are beginning to be more numerous near the cortex of the fractured end. The chondrocytes are beginning to line up in a fashion similar to that seen in epiphyseal growth in the



young animal. The chondrocytes are more numerous than at any later stage, and a very large number of them are hypertrophic. Osteoblasts are beginning to appear along the edges of the trabeculae, and the marrow cavity is beginning to extend into the callus (fig. 5).

On the eighteenth day the chondrocytes are in rather regular alignment with the calcified strands extending from the irregular network into the lines of deposition between the columns of cartilage cells. The network is everywhere continuous with the cortex and fills out all of the callus with the exception of the very central zone, made up of the



Fig. 5.—Fifteenth day: large mass of cartilage cells, most of which are at this stage swollen and hyperchromatic. At the periphery of this clump the forming trabeculae may be seen. Hematoxylin and eosin;  $\times 125$ .

columns of cartilage cells. Many osteoblasts and a few osteoclasts may be seen with numerous transitional forms between the chondrocytes and these bone elements.

On the twenty-first day the entire callus is a mass of irregularly calcified trabeculae with, here and there between, small clumps of hypertrophic cartilage cells, containing hyperchromatic nuclei. The cortex proper has been resorbed quite far back from the line of fracture, and the network of the trabeculae seems to be continuous with the

"flared" end of this cortex. The entire callus has begun to shrink in size and the cartilage cells to decrease in number, and into the spaces between the trabeculae farthest from the fracture line, normal bone marrow cells are beginning to appear. At the fracture site there is still a dense, close, calcified network inclosing some hypertrophic cartilage cells (fig. 6).

On the twenty-fourth day there is marked encroachment of, first, capillaries and, behind that, bone marrow toward the line of fracture.

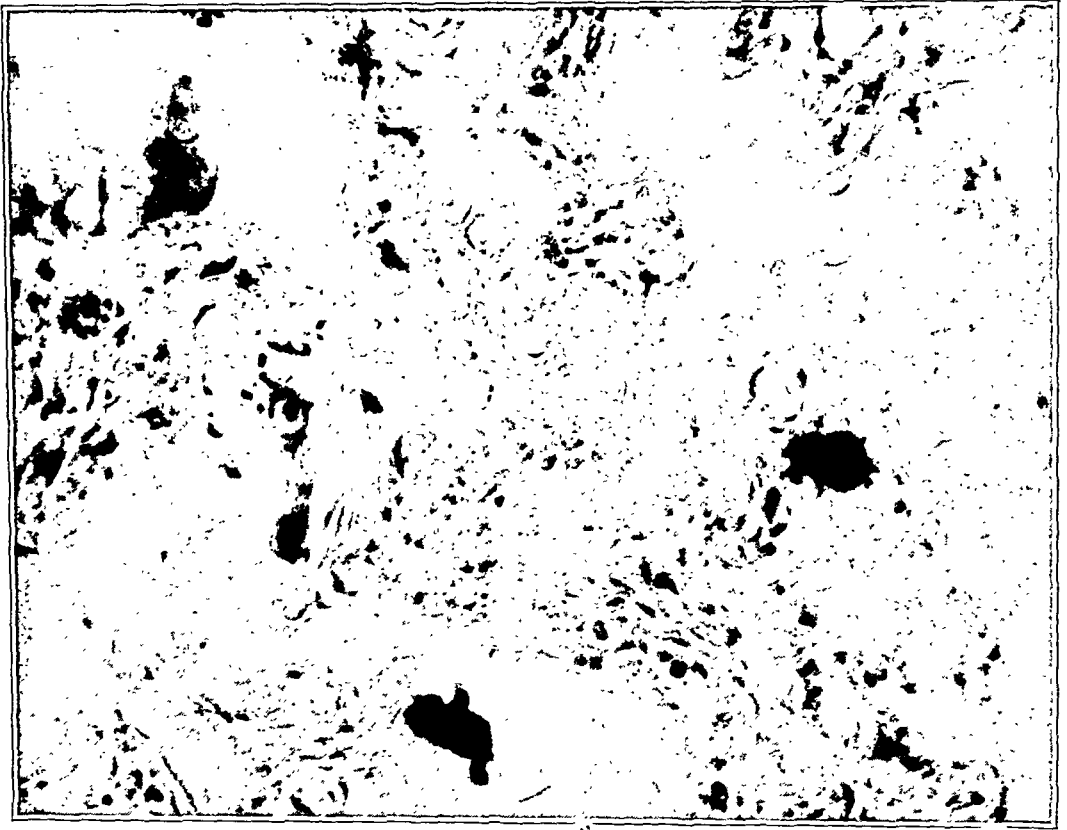


Fig. 6.—Twenty-first day: irregular mass of forming trabeculae, with stages between hypertrophic chondrocytes and osteoblasts apparent. Hematoxylin and eosin;  $\times 300$ .

There is a marked decrease in the diameter of the callus with an increase in the size and density of the trabeculae.

On the twenty-seventh day the newly formed trabecular network completely joins across the line of fracture, with the chondrocytes almost entirely gone. The trabeculae are beginning to fuse near the periphery and farthest from the line of fracture.

On the thirtieth day the trabeculae across the fracture line are more marked, and practically all of the spaces contain essentially normal bone

marrow cells. The edges of the trabeculae contain many osteoblasts and osteoclasts, the result of the rapid changes of ossification.

On the thirty-third day there is a marked increase in the size of the newly formed marrow spaces near the center of the healing bone, with a decrease in their size near the periphery. Coincident with this, there is an increase in the number, size and density of the trabeculae near the periphery and directly continuous with the old cortex, and a complementary decrease nearer the center where the larger marrow spaces are to be found.

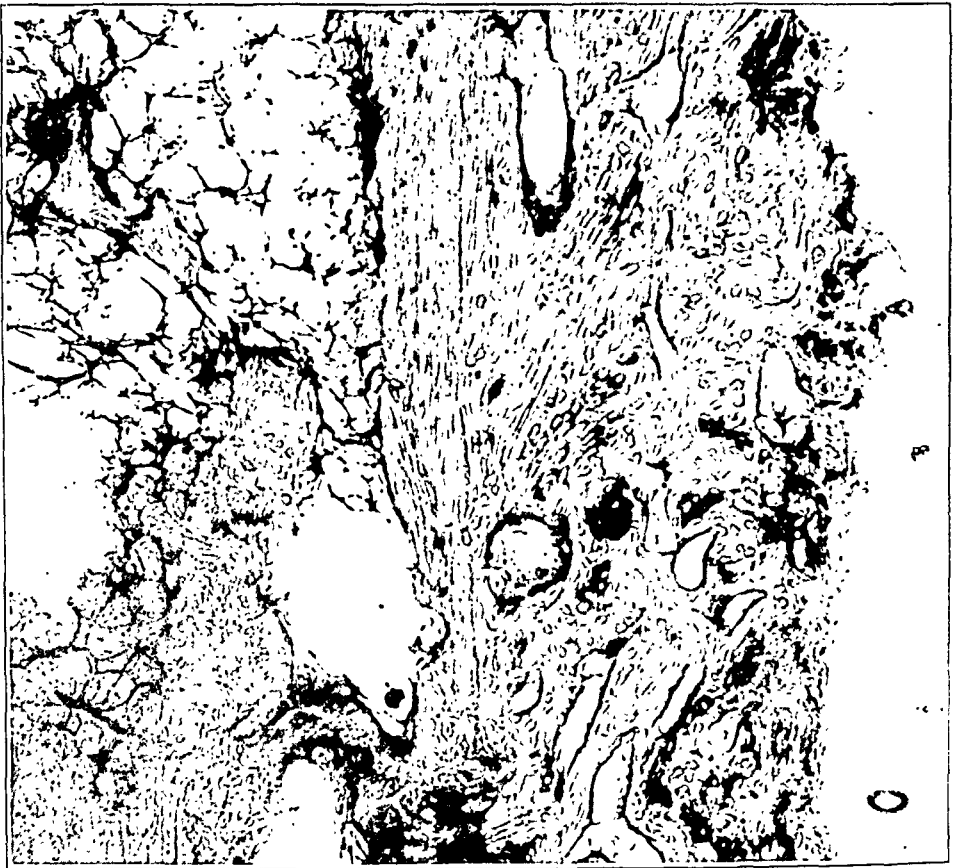


Fig. 7.—Thirty-sixth day: massing of trabeculae to form the new cortex. The medullary cavity is not yet complete. The new cortex is highly cellular and vascular. Hematoxylin and eosin;  $\times 125$ .

On the thirty-sixth day these processes are continuous. There is, by this time, an almost complete new cortex, thicker, less dense than in the older portion and with the osteocytes large, hyperchromatic and in many loci apparently syncytial (fig. 7).

On the thirty-ninth day the marrow cavity is practically continuous through the site of the fracture. There is only a slight bulge to mark the site of the old cavity, and the cortex is still slightly thicker and contains numerous hyperchromatic osteocytes.

On the forty-second day the changes are still proceeding toward the preoperative conditions. Only an occasional incomplete trabecula may be seen in the medullary cavity. The cortex is only slightly thicker and less dense than is the case away from the line of fracture.

From the forty-fifth to the fifty-first day no particularly notable changes may be seen. On the fifty-first day, aside from a slight irregularity in outline, no difference may be seen between the architecture and histology at the old fracture site and elsewhere along the shaft of the bone (fig. 8).

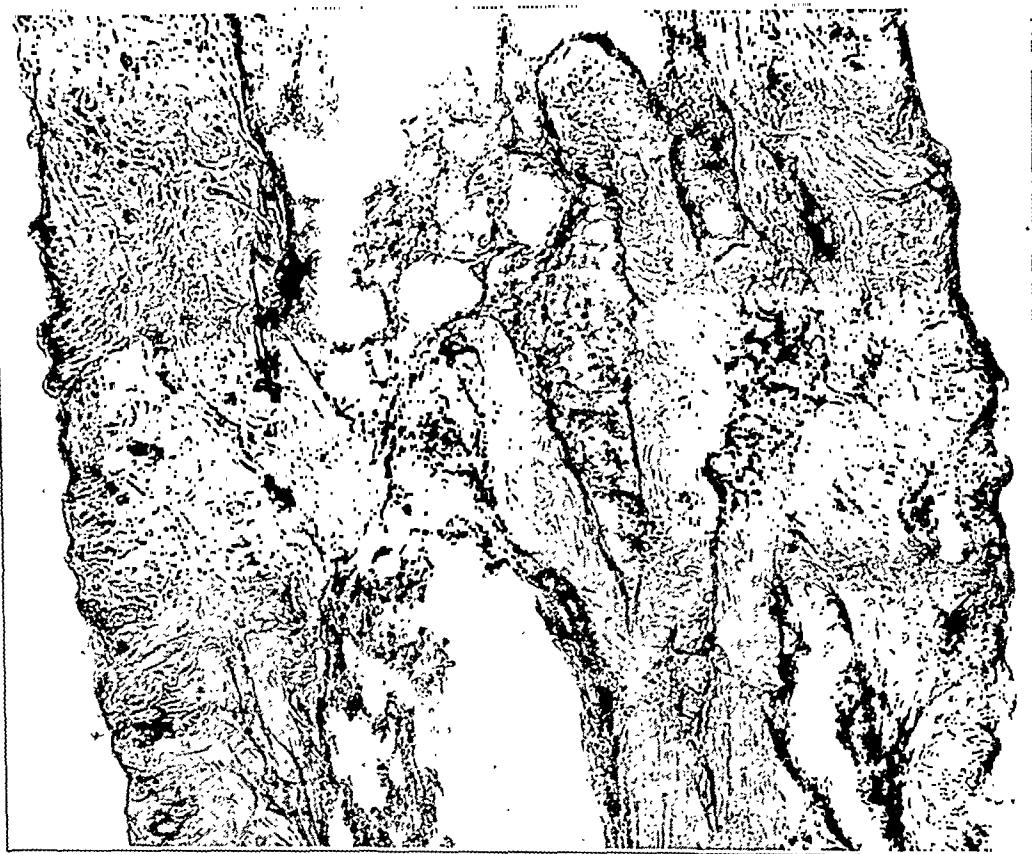


Fig. 8.—Forty-fifth day: marrow cavity reestablished, cortex practically complete, less cellular, less vascular. Normal contour and thickness are almost obtained. Hematoxylin and eosin;  $\times 125$ .

#### COMMENT

Bast<sup>6</sup> gave an excellent and detailed account of the histologic processes involved in bone repair in rabbits. Our study does not agree in all respects with his, particularly in that the entire series of changes observed by him had taken place with greater rapidity than was the case with our animals. It is felt, however, that the difference in species

6. Bast, T. H., and Sullivan, W. E.: *Anat. Rec.* **31**:255, 1925.

of animals and the entirely different methods of attack on the problem accounts for the lack of complete agreement in results.

Our own histologic studies on the healing of fractured fibulae in rats on a standard, well balanced diet agree closely with the series of events described by Maximow and by Häggqvist. Immediately after fracture, the site of the lesion fills in with blood from the ruptured small vessels. This blood clot is replaced within a matter of hours by a fibrin clot containing numerous lymphocytes. Soon these are replaced in the preparation by fibroblasts, and the clot has become a fibrous connective tissue callus, continuous with both the endosteum and the periosteum of the two fractured ends. At first, a few of these fibroblasts at the periphery become chondroblasts. As these become more numerous, the fibrous callus is gradually replaced by a cartilaginous callus.

Coincident with these changes, the old cortex is beginning to break up, and these decalcifying fragments, surrounded by multinucleated clumps of protoplasm (osteoclasts), may be seen in the callus nearest the cortical ends. In succeeding preparations, these fragments become less and less numerous, until by the twelfth day they are no longer seen. Before this series of events is complete, the older cartilage cells (chondrocytes) are beginning to assume the appearance of osteoblasts, and very irregularly distributed and formed clumps of calcifying protoplasm appear throughout the callus. As these increase in size, they merge into each other, and by the time the callus is well filled in by calcified strands the process of resorption or medullation has begun and the so-called "osteoclasts" again are seen.

At the next stage the cortex has become continuous over the site of the fracture and the medullary cavity is likewise reunited. Soon the entire bone has returned to practically its original form. From this stage on, the changes that take place in the production of normal, adult bone probably are in operation in the direction of Wolff's law of function governing form.

As has been said, Häggqvist does not believe that the osteoclasts in themselves are responsible for bone resorption. He has further postulated that in this process some other phenomena are responsible for the resorption of the bone salts and that the so-called "osteoclasts" are but a small amount of protoplasm with the clumped nuclei of the osteocytes that have remained behind after resorption has taken place. In other words, they constitute a residuum of decalcified bone.

Up to this point, we can go with Häggqvist almost without reserve. He further believes, however, that these so-called "osteoclasts" probably have no phagocytic powers. This we believe is open to question. A fine definition is here needed to determine what may be classed as phagocytic bone cells. That the basic protoplasm of bone enters into the

protoplasm of these cells and is in turn given up again to the blood stream seems to be fairly evident. This process is perhaps not phagocytosis in the strictest sense of the word. That these cells do not have the power of breaking down matured calcified bone, of ingesting particles of calcified bone, in spite of Jordan's<sup>7</sup> views to the contrary, we feel convinced is the correct view.

Up to this point, we have been relying on the studies of purely morphologic anatomy and histology, and here we must confess that we arrive at a dead end in our reasoning. It is now, however, that the studies of Pond<sup>8</sup> in this direction have amply demonstrated that, while the laying down of the organic matrix of bone—the formation of the collagenous protoplasm—is the function of connective tissue metabolism, the actual calcification, the conversion of the organic calcium, phosphorus and other salts to their inorganic forms in mature calcified bone is a purely physicochemical process of crystallization of these salts into the collagenous matrix. This chemical process is probably wholly independent of the cellular make-up of the tissues except for the need for the laying down of the proper chemically constituted matrix.

In the studies made on the breaking strengths of the healing fractured fibulae, it was observed that the primary callus was formed by the fifteenth day, at which time the callus strength was at a high level. Subsequently strength was lost rapidly until the twenty-first day, which was attributed to the development of the medullary cavity. This was followed by a gradual return to normal strength on the forty-fifth day through cortical thickening and reorganization of the callus.

Our histologic studies indicate that by the fifteenth day, when strength was at its initial highest rise, the hypertrophic chondrocytes were present in large numbers and calcification advanced. In explanation of the calcification at this period, the work of Fell and Robison<sup>9</sup> on avian embryonic limb buds strongly indicates that the hypertrophic cartilage cells are the source of a phosphoric esterase, which they termed phosphatase. To this enzymotic substance, they attributed the hydrolysis of the organic phosphates to the inorganic form found in bone.

It is at least possible, from the histologic picture that we noted on the fifteenth day, that the chondrocytes, which are in a hypertrophic state, are elaborating an abundance of phosphatase with the result that the calcific state is at its optimum and the strength of the callus at the high point observed.

The sharp loss of strength found to occur between the fifteenth and twenty-first day necessitates careful study. In an interval of nine days,

7. Jordan, H. E.: *Anat. Rec.* **20**:281, 1921.

8. Pond, S. E.: *Internat. J. Orthodontia* **14**:369, 1928.

9. Fell, H. B., and Robison, R.: *Biochem. J.* **23**:767, 1929.

the strength diminishes roughly 40 per cent. This cannot be associated only with the fusing of the ingrowing blood vessels that were noted grossly, but, on the contrary, some chemical factor of considerable power has come into the field and destroyed the unity of the calcified mass. That this is a blood substance is apparent when we consider that the skeleton in general simultaneously shows a rapid loss in strength. The decalcifying ability of the parathyroid hormone has been clearly demonstrated by Aub and his co-workers<sup>10</sup> in the treatment for chronic plumbism, as well as by Jaffe and Bodansky<sup>11</sup> in the experimental production of osteitis fibrosa cystica. That this may be the substance responsible for weakening the strength of the callus we can only assume, but in the face of our present knowledge the hypothesis is at least attractive. The chondrocytes are apparently deleteriously affected by the activity of the decalcifying substance, for their nuclei show a definite hyperchromatosis. It is not entirely unreasonable, then, to assume that the tentative suggestion of Kay<sup>12</sup> that an antagonism exists between phosphatase and possibly the parathyroid hormone is highly probable. Whatever the strength-reducing factor may be, its activity rapidly diminishes after the twenty-first day. Subsequently the development of true bone proceeds at a uniform rate, to attain its end-point on the forty-fifth day.

As more and more studies on the skeletal system are made, the high degree of plasticity it possesses becomes increasingly obvious. Collip<sup>13</sup> may be said to have first indirectly called our attention to this, and the studies made on the breaking strength of bone have borne it out. Connective tissue forms an extremely labile and changeable tissue. However, in a sense we still remain in the dark as to the stimulus initiating the various cytologic steps that we have observed. The impulse we do not know. It may be an amino-acid formed at the fracture site or it may be merely a disturbed physicochemical balance, but whatever it is we believe that the next few years will see a decided advance in our knowledge of bone.

#### SUMMARY

The cytologic processes involved in the healing of fractured fibulae in rats reveal the fundamental soundness of the views of Maximow and of Häggqvist as to the inherent abilities of connective tissue cells to

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10. Aub, J. C., and Hunter, D.: *Quart. J. Med.* **20**:123, 1927. Bauer, W.; Aub, J. C., and Abrecht, J.: *J. Exper. Med.* **49**:145, 1929.

11. Jaffe, H. L., and Bodansky, A.: *J. Exper. Med.* **52**:669, 1930.

12. Kay, H. D.: Personal communication to R. M. McKeown, 1931.

13. Collip, J. B., in *The Harvey Lectures, 1925-1926*, Baltimore, Williams and Wilkins Company, 1927. Collip, J. B.; Clark, E. P., and Scott, J. W.: *J. Biol. Chem.* **63**:439, 1925.

change from one type to another under proper stimulus. Further, one may see adequate evidence of the physicochemical processes involved in bone healing—if the preparations are studied with this in mind.

The healing of bone on standard diets reveals the process to be divisible into the following stages:

1. A fibrinous clot, lasting until about three days after fracture.
2. A fibrous clot or callus, beginning to replace the fibrinous clot at about the second day after fracture and lasting until about the twelfth day.
3. A cartilaginous callus, beginning at about the sixth day and lasting until about the twenty-seventh day.
4. A calcifying callus, beginning almost coincidently with the formation of hypertrophic cartilage, reaching its greatest mass density at about the fifteenth day and following very closely the development and recession of the cartilage mass.
5. Last, the stage of ossification, beginning about the twenty-first day, that is, overlapping the stage of calcification and following through the later changes in the hollowing out of the marrow cavity, the organization of the cortex and the remodeling of the reformed bone.

A positive correlation has been shown to exist between the cytologic picture and the breaking strength of the healing callus at different time periods from the inception of the fracture to the restitution of its normal histologic structure and strength.

A histologic control or base line is established for comparison with the changes found in the healing of fractured bones of animals on different types of unbalanced diets.



# HISTOLOGY OF HEALING FRACTURES IN RATS ON DIETS LOW IN TOTAL SALT, CALCIUM AND PHOSPHORUS

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Previous reports by Lindsay and Howes,<sup>1</sup> McKeown, Lindsay, Harvey and Lumsden,<sup>2</sup> and Downs and McKeown<sup>3</sup> have dealt with the breaking strength and histology of fractured fibulae in rats on normal and synthetic diets. The present study deals similarly with variations observed microscopically in the fractured fibulae of these animals when the salt content of their diet was markedly altered.

## METHOD

As in the previous studies, the animals were placed on the diet utilized for one week, at the expiration of which time the right fibula was fractured in the manner described before.<sup>1</sup> Two animals from each dietary group were killed at the following postoperative time periods: six, twelve, eighteen and twenty-four hours. Two animals were also killed one, two, three, four, five and six days postoperatively and thereafter at three day intervals to and including fifty-one days. After death the legs were removed, and the tibiae and fibulae cleaned of all adhering soft tissue, and the bones then fixed in a dilute solution of formaldehyde U. S. P., 1:10. After ten days' fixation, they were decalcified in a 5 per cent solution of nitric acid in the diluted solution of formaldehyde, washed and embedded in celloidin. Later that portion of the fibula containing the fracture was sectioned longitudinally and stained with hematoxylin and eosin, Mallory's connective tissue stain or Masson's triple stain. However, after familiarity with the material had been gained, simple hematoxylin-eosin stain was the one generally adhered to. By sectioning the diaphysis longitudinally, a complete picture of the fracture at different levels was obtained.

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The expenses of this investigation were defrayed in part by Davis and Geck, Inc.

From the Department of Pathology and Department of Surgery, Yale Medical School.

1. Lindsay, M. K., and Howes, E. L.: The Breaking Strength of Healing Fractures, I, J. Bone & Joint Surg. **13**:491, 1931.

2. McKeown, R. M.; Lindsay, M. K.; Harvey, S. C., and Lumsden, R. W.: The Breaking Strength of Healing Fractured Fibulae of Rats, II, Arch. Surg. **24**: 458 (March) 1932; others to follow.

3. Downs, W. G., Jr., and McKeown, R. M.: The Histology of Healing Fractures in Rats on a Normal Diet, Arch. Surg., this issue, p. 94.

For this series of studies, the diet utilized was the standard diet developed by Moise and Smith,<sup>4</sup> with the salt content varied as outlined by Osborne and Mendel.<sup>5</sup>

On each of the three diets 100 mg. of dried yeast powder was fed every second day, and antiscorbutic rations were given in large quantities at frequent intervals. It will be noted that the basic diets were not lacking in vitamin content.

### HISTOLOGY

There was little difference cytologically between the fractures of the "standard" or normal diet animals<sup>3</sup> and those on the various low salt

TABLE 1.—*Standard or Basic Diet*

	Per Cent	Calories per Kilogram of Food	Apportionment of Total Calories, per Cent
Casein.....	18	738	Protein..... 13.8
Starch.....	51	2,091	Carbohydrate 39.2
Crisco.....	22	2,046	
Cod liver oil.....	5	465	Fat..... 47.0
Salts (varied according to the diet being fed).....	4		
	100	5,340	100.0

TABLE 2.—*Salt Content of the Different Diets*

	Low Calcium Diet	Low Phos- phorus Diet	Low Total Salt Diet
Calcium carbonate .....	0.00	12.24	No salt
Magnesium carbonate .....	2.42	1.21	mixture
Sodium carbonate .....	5.80	1.71	whatsoever
Potassium carbonate .....	14.13	3.53	was added
Orthophosphoric acid .....	3.72	0.00	to the
Hydrochloric acid .....	5.34	5.34	basic diet
Sulphuric acid .....	0.92	0.92	
Citric acid and water.....	11.11	9.50	
Ferric citrate, 1½ water.....	0.634	0.634	
Potassium .....	0.002	0.002	
Manganese sulphate .....	0.0079	0.0079	
Sodium fluoride .....	0.0248	0.0248	
Alum .....	0.00245	0.00245	
Lactose .....	246.00	246.00	

diets during the first six days postoperatively. Immediately following the fracture, a blood clot formed in and about the fractured bone. This changed within eighteen hours into a clot largely fibrinous in character in which many lymphocytes, but only the shadows of erythrocytes, were observed. By the end of forty-eight hours the clot had become a well defined callus made up entirely of fibrin and lymphocytes, uniting the fractured ends within its body. At this stage, the individual cells of the periosteum and endosteum could easily be seen. On the third day, the periosteal and endosteal cells were undergoing proliferation, and the lymphocytes within the clot were being replaced by young fibroblasts.

4. Moise, T. S., and Smith, A. H.: J. Exper. Med. **40**:13, 1924.

5. Osborne, T. B., and Mendel, L. B.: J. Biol. Chem. **34**:131, 1918; **37**:557, 1919.

On the fourth day, the callus consisted entirely of fibroblastic connective tissue continuous with the periosteum and the endosteum. It completely filled the marrow cavity for some distance in each direction from the fractured line, and showed a tendency to condense across the fracture gap. A few large multinucleated osteoclasts could be seen by this time along the margins of the still partially calcified trabeculae within the bone marrow and near the cortex. On the fifth day, there was further condensation in the fibrous callus through the path of the fracture. In addition it was observed that a proliferation of vessels and capillaries was occurring. It was further noted that in and around these capillary buds or tufts irregular depositions of calcium salts were developing. Simultaneously, many of the fibroblasts in the body of the callus increased in size and assumed a shape roughly spherical. These latter cells were young chondroblasts, and their number differed somewhat in the animals on the three diets studied. The presence of the chondroblasts was, in general, especially notable near the periphery of the line of fracture. The nuclei of the osteocytes in the cortex and trabeculae at this stage appeared slightly hyperchromatic, and it was seen that fragmentation and dissolution of the bone about these areas of hyperchromatosis was manifesting itself, particularly so in the distal end of the shaft of the fractured fibula. On the sixth day, the condensation of the fibroblasts directly in the midline of the fracture, as well as in its periphery, was continuous with the periosteum. It was also observed that, except in the animals on the diet low in calcium, young cartilage cells were beginning to appear in considerable numbers through the superior planes of the callus. From this stage on, the processes observed differed somewhat in the animals on the three types of diets studied and may be described to advantage as separate entities.

#### 9 Days

##### Low Salt

Definite clumps of cartilage cells, none as yet hypertrophic, beginning of fibrous trabeculation, but with no calcification apparent; decalcification of ends of cortex

##### Low Calcium

Callus largely dense fibrous connective tissues; no trabeculation; some fragmentation of cortex; few or no osteoclasts and no chondroblasts

##### Low Phosphorus

Quite dense connective tissue callus; a few cells away from line of fracture and near periphery beginning to have "swollen" appearance and larger and hyperchromatic nuclei. Occasional chondroblasts seen

#### 12 Days

Large clumps of cartilage, many cells hypertrophic; decalcification of cortex and of fragments but no calcification of fibrous trabeculae

Largely fibrous connective tissue; a few fibroblasts beginning to look swollen; a few osteoclasts at ends of cortex; beginning condensation into fibrous trabeculae

Chondrocytes are more numerous, especially near periphery and away from fracture line; network of dense fibrous connective tissue well formed except across fracture line

15 Days

Callus almost entirely hypertrophic cartilage; slight calcification of trabeculae; marked decalcification of fragments in cortex; no calcification of trabeculae or fibrous connective tissue across fracture line (fig. 1)

Cartilage cells fairly numerous through fracture line especially; decalcification of cortical ends quite marked; further condensation of fibrous connective tissue trabeculae in which there is no evidence of calcification (fig. 2)

Chondrocytes and chondroblasts present in large masses near the fracture line, except in center; bony ends and fragments being rapidly absorbed; many multinucleated masses, osteoclasts present in this central region; no evidence of calcification (fig. 3)

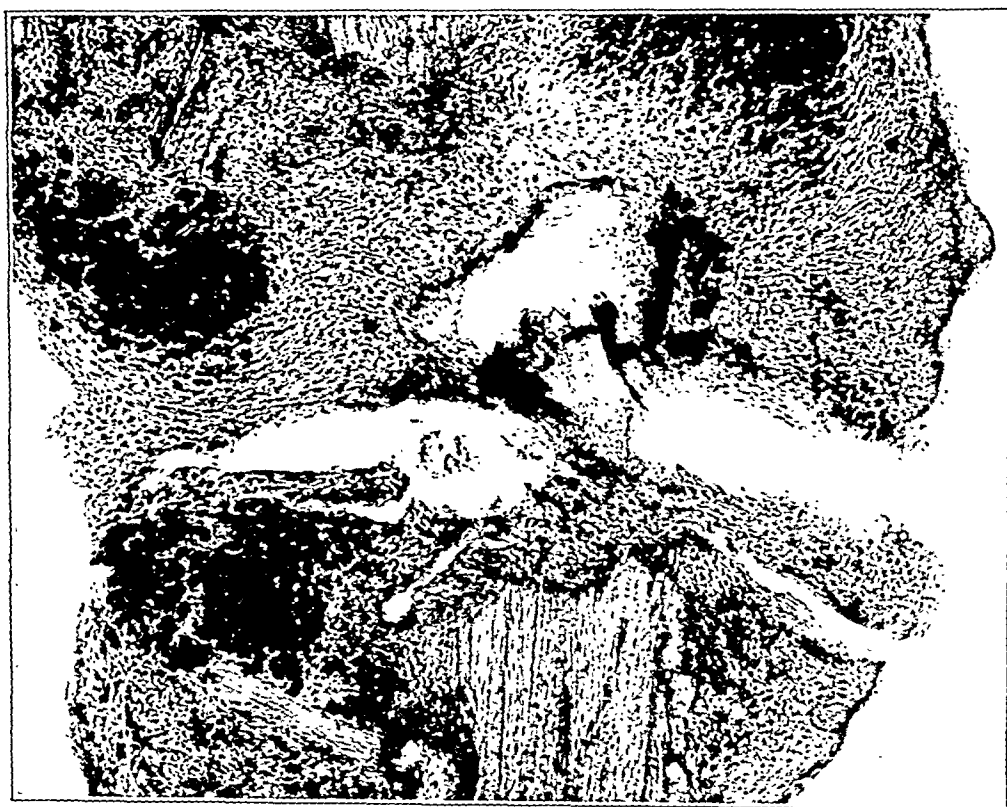


Fig. 1.—Photomicrograph of fractured fibula of animal killed after fifteen days on a low salt diet, showing large amounts of cartilage, fibrous callus and decalcification of ends of cortex;  $\times 75$ .

18 Days

Large numbers of hypertrophic cartilage cells irregularly arranged; no great change from fifteen day period

Further condensation of trabeculae, with little evidence of calcification; marrow cavity extending closer to line of fracture

Picture essentially unchanged, except that marrow cavity is beginning to encroach on masses of connective tissue and cartilage in fracture line

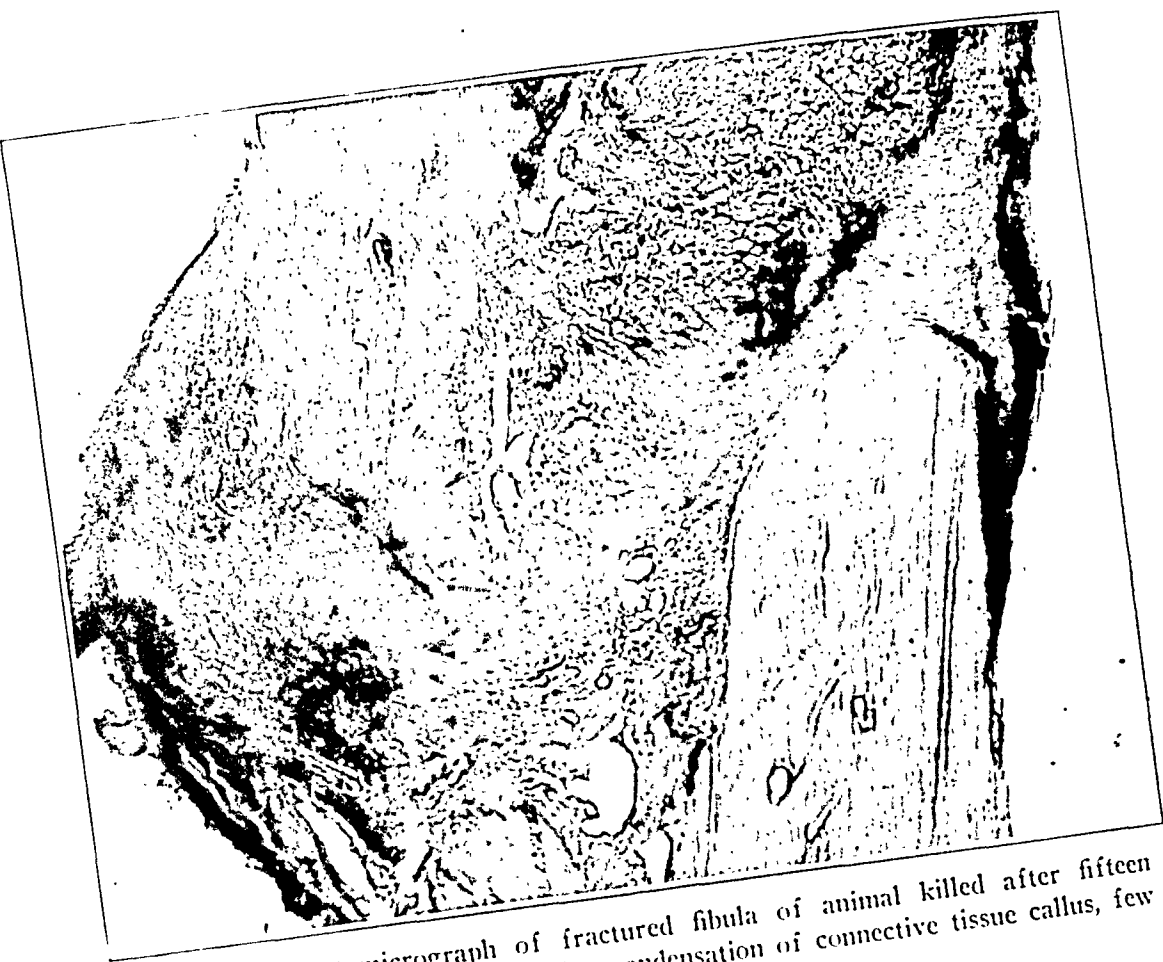


Fig. 2.—Photomicrograph of fractured fibula of animal killed after fifteen days on a low calcium diet, showing condensation of connective tissue callus, few cartilage cells and no evidence of calcification;  $\times 75$ .

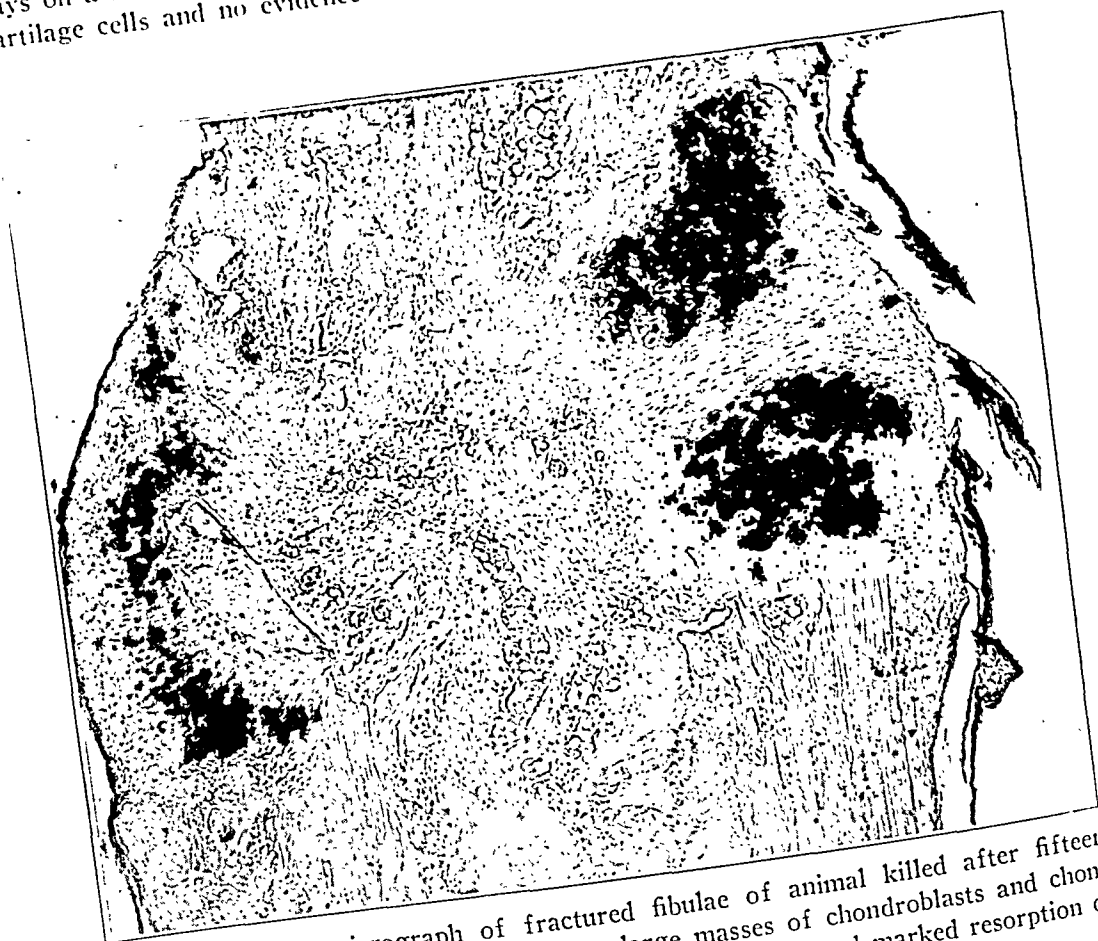


Fig. 3.—Photomicrograph of fractured fibulae of animal killed after fifteen days on a low phosphorus diet, showing large masses of chondroblasts and chondrocytes, especially near periphery of the line of fracture, and marked resorption of the cortex of the trabeculae;  $\times 75$ .

## 21 Days

Less cartilage, some calcification of trabeculae which are invading cartilaginous mass at fracture line (fig. 4)

More condensation of trabeculae; distinct effort to form a thin cortex; not greatly calcified (fig. 5)

An almost complete disk of cartilage can be seen filling fracture line and extending each way up into marrow cavity and adjacent to bone marrow cells; very little fibrous connective tissue remains (fig. 6)



Fig. 4.—Photomicrograph at the twenty-one day period, low salt diet, showing only small amount of cartilage, fibrous trabeculae invading callus and some calcification of trabeculae;  $\times 75$ .

## 24 Days

More trabeculae, only slightly calcified; considerable numbers of hypertrophic cartilage cells remaining

Uncalcified connective tissue cortex and trabeculae beginning to fuse across fracture line

Picture essentially unchanged; hypertrophic cartilage cells not conspicuous; little evidence of decalcification; none of calcification

## 27 Days

Many cartilage cells remaining; larger numbers of trabeculae; slight calcification

Still many cartilage cells in fracture line and near it; little evidence of calcification

Little change; cartilaginous disk still fills line of fracture; possible slight condensation of shaft



Fig. 5—Photomicrograph at the twenty-one day period, low calcium diet, showing condensation of trabeculae, formation of thin cortex and little or no calcification;  $\times 75$ .

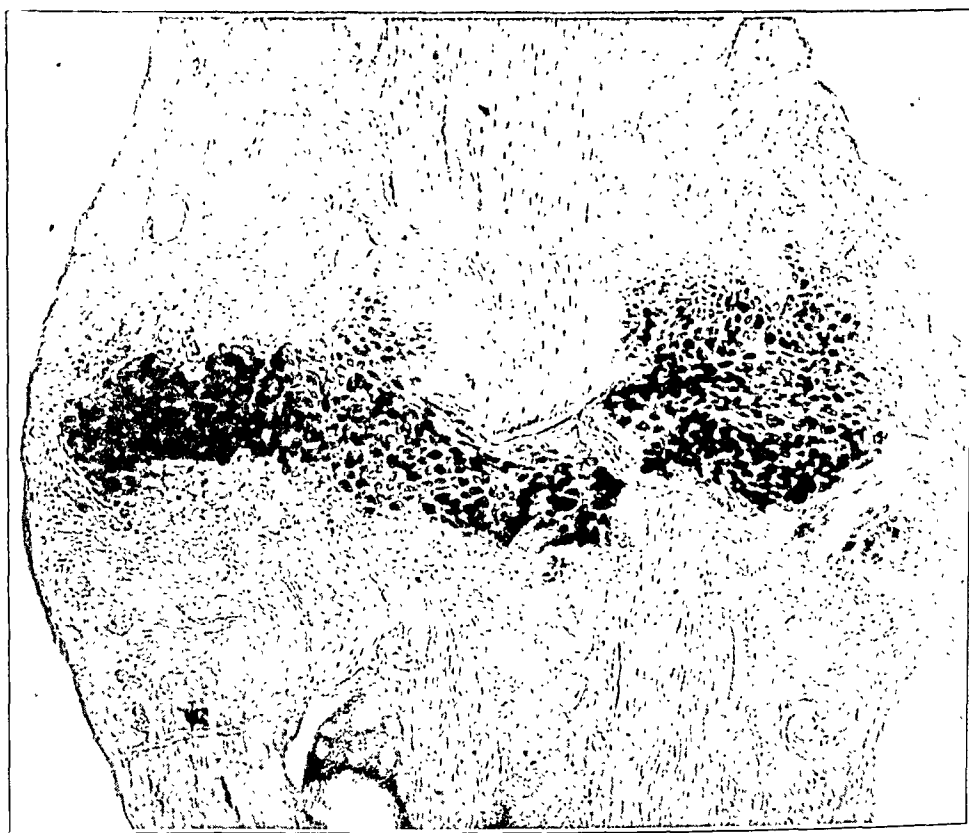


Fig. 6.—Photomicrograph at the twenty-one day period, low phosphorus diet, showing nearly complete disk of cartilage through line of fracture, little fibrous tissue present and trabeculae forming outside mass of cartilage;  $\times 75$ .

30 Days

No marked change; trabeculae calcified up to mass of cartilage which still formed fracture line; this is making an effort to line up in a fashion similar to growth in the epiphyses of young bones

Little change; decalcification still obvious; further condensation of trabeculae, but little evidence of calcification

Slight changes only; in some places cells are apparently going back from cartilage to an earlier fibrous connective tissue type of cell

33 Days

No particular changes

Conditions little changed; slight evidence of calcification; cortex more complete across fracture line

Slight if any changes in fracture line; cortex slightly more dense and mature-appearing away from fracture line; cartilaginous disk still complete

36 Days

Some condensation of trabeculae at sides near cortex, but still little invasion of cartilaginous callus

Architecture nearly normal, but little evidence of calcification in new-formed cortex and trabeculae; no cartilage to be seen

No appreciable changes from preceding period

39 Days

No marked change; greater condensation of trabeculae in cortex away from cartilaginous callus (fig. 7)

Essentially unchanged (fig. 8)

Disk of cartilage still apparent between fractured ends; slightly greater encroachment of dense connective tissue trabeculae into cartilage; picture very similar to that of epiphysis in marked rickets (fig. 9)

42 Days

Trabeculae have broken through the cartilaginous callus in line of fracture; some evidence of calcification of these trabeculae in cortex

Slightly more evidence of calcification; cortex very cellular; areolae around bone cells very large, and the cells themselves are also large and pale looking

Disk of cartilage thinner; connective tissue trabeculae encroaching into this disk; only slight evidence of calcification of these encroaching trabeculae





Fig. 7.—Photomicrograph at the thirty-nine day period, low salt diet, showing trabeculae condensed near fracture line, but much cartilage still present, and considerable calcification;  $\times 75$ .

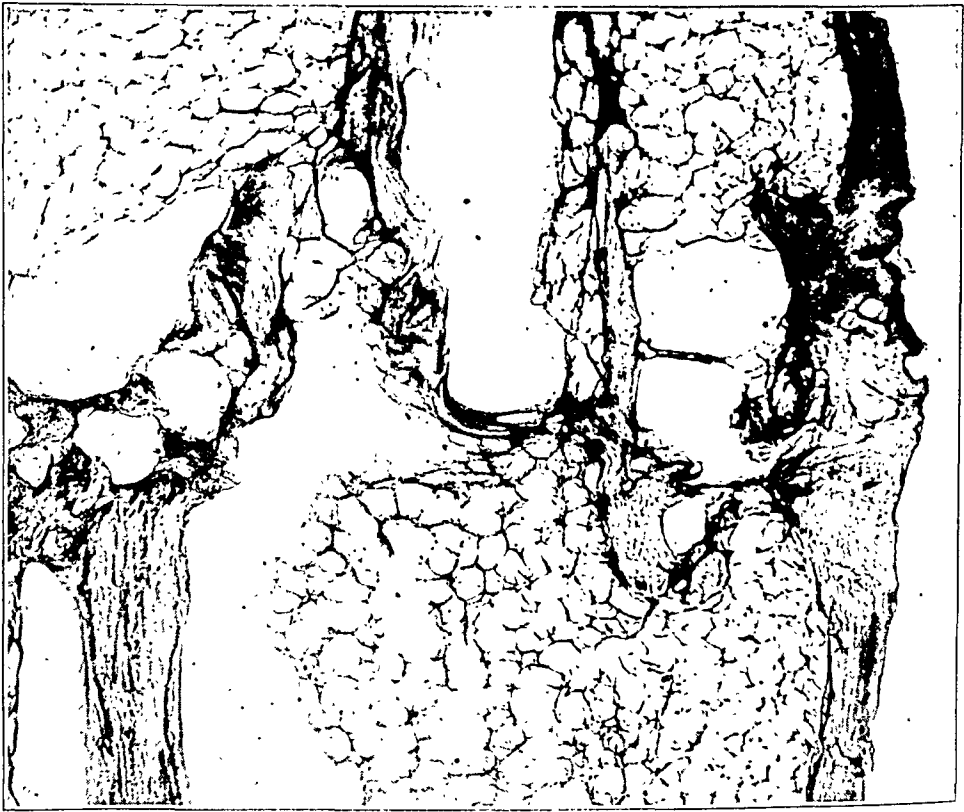


Fig. 8.—Photomicrograph at the thirty-nine day period, low calcium diet, showing architecture nearly restored, but very light and thin and poorly calcified, an absence of bone marrow cells in this region, and an irregular cortex;  $\times 75$ .

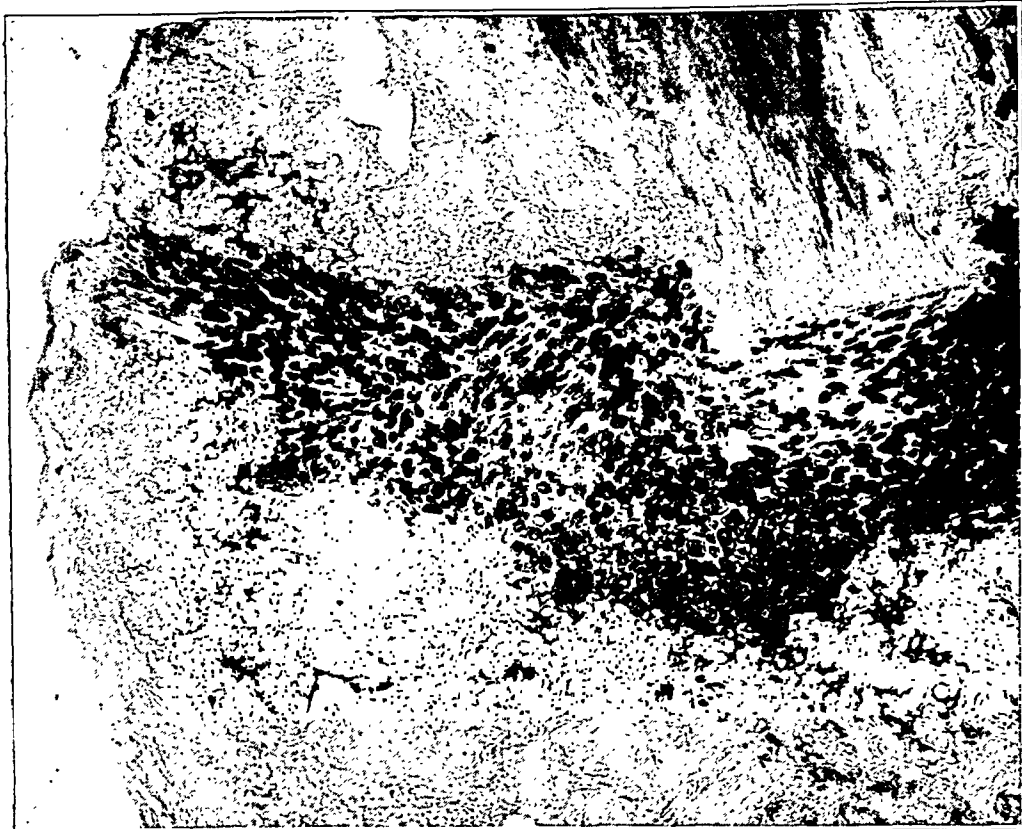


Fig. 9.—Photomicrograph at the thirty-nine day period, low phosphorus diet, showing complete disk of cartilage still apparent across fracture line giving a picture very similar to that of epiphyses in rickets;  $\times 75$ .



Fig. 10.—Photomicrograph at the forty-five day period, low salt diet, showing cortex and trabeculae thick, but still quite cellular, definite calcification and the presence of bone marrow cells;  $\times 75$ .



Fig. 11.—Photomicrograph at the forty-five day period, low calcium diet, showing architecture well restored, cortex not well differentiated, little calcification and no marrow cells;  $\times 75$ .



Fig. 12.—Photomicrograph at the forty-five day period, low phosphorus diet, showing cartilaginous disk still not displaced with invasion by amorphous-looking connective tissue and no evidence of calcification in callus proper;  $\times 75$ .

45 Days

Modelling or medullation beginning; cartilage nearly gone (fig. 10)	Cortex slightly thicker, denser, better calcified (fig. 11)	Cartilage being irregularly displaced by a rather amorphous looking mass of connective tissue; very slight evidence of calcification (fig. 12)
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48 Days

Cortex thicker; trabeculae more massed; more advanced calcification	Essentially unchanged; cortex somewhat thicker, more complete; calcification still only slight	Marrow cavity partly extended through callus; cartilage cells can still be seen in the irregular cortex
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51 Days

Architecture practically restored; cortex fragile but complete; only few remaining trabeculae; these and cortex highly cellular	Cortex at fracture line still not well calcified, quite cellular; architecture essentially restored	Similar to 48 day period; marrow cavity somewhat larger; cortex slightly more dense and compact, still extremely cellular; a few chondrocytes can still be seen scattered through the callus
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COMMENT

It is quite obvious from a study and analysis of this series of histologic preparations that changes in the healing fractures of animals on a low salt diet follow, in general, the changes described in fractures of rats on a standard diet,<sup>3</sup> but with a general retardation of the entire reparative process. However, marked variations are to be found in the fractured fibulae of animals on low calcium and low phosphorus diets. In the case of the animals on the low calcium diet, the outstanding picture is the general delay in the calcific processes. The cellular responses involved in the low calcium fractures are similar in order of appearance to those in the normal animals, but are again so retarded as to be almost absent until late in the healing reaction.

The cytologic response to a low phosphorus diet, on the other hand, is characteristic. Here cartilage formation begins at about the time that it is found in the animals on normal diets, but progresses much more rapidly to form a complete disk through the line of fracture, which apparently becomes a definite obstacle to the ingrowth of normal bone. More and more this cartilaginous disk simulates the picture seen in the rachitic epiphyses.

In work reported elsewhere,<sup>6</sup> it has been shown that the curve of the healing strength of fractured rat fibulae gains its first peak on the fifteenth day of healing, falls thereafter for six days, and subsequently gains an end point with strength nearly restored by the forty-fifth day. The strength of the healing fracture is largely, but by no means entirely, attendant on the extent of calcification of the callus, and it was with this that we were primarily concerned in the present studies.

Calcification of a fracture follows the development of cellular elements in the fracture, and apparently is the result of their activity. Fell and Robison<sup>7</sup> expressed the belief that hypertrophic cartilage cells, such as were found in our studies, are the precursors of an esterase-phosphatase, through the activity of which calcium phosphate compounds are precipitated. One of us<sup>8</sup> (Dr. McKeown) has been able to demonstrate in fractured rat fibulae that following fracture this esterase first increases locally and later decreases fully as rapidly as it rose. By the time the primary callus has formed on the fifteenth day the phosphatase content was diminished, and, with the sharp reduction in callus strength between the fifteenth and twenty-first days, phosphatase was restored to a level nearly that of normal. Later, as the callus strength again rose, eventually becoming equal to the normal, the phosphatase apparently varied but slightly.

It is somewhat difficult to conceive of phosphatase being a product entirely of cartilage cells, as Fell and Robison<sup>7</sup> suggested. If such were the case, phosphatase should be at its highest level after the fifteenth day, and the callus strength proportionately greater. Murray<sup>9</sup> is of the opinion that phosphatase is not the product of hypertrophic cartilage, but of the death of tissue cells. This is an attractive hypothesis and one that he has studied carefully, but tissue death is evidently not productive of the optimal alkaline hydrogen ion concentration, which we have found essential for the hydrolytic reaction of phosphatase; rather, it is apparently productive of an acidic state inhibitory to the phosphatase.

It would seem that the possibility expressed elsewhere that phosphatase is antagonized by parathyroid hormone is more attractive as a hypothesis.<sup>2</sup> The cartilage cells could form phosphatase, but at a certain stage the activity of the esterase would be inhibited by the hormone. The reason for the inhibitory state developing on or about the fifteenth day we do not know, but evidently it does so regardless of the diet or other treatment.

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6. Lindsay and Howes (footnote 1). McKeown, Lindsay, Harvey and Lumsden (footnote 2). Downs and McKeown (footnote 3).

7. Fell, H. B., and Robison, R.: *Biochem. J.* **23**:767, 1929

8. McKeown, R. M., and Ostergren, J. I.: *Proc. Soc. Exper. Biol. & Med.* **29**:54 (Oct.) 1931.

9. Murray, C. R.: Personal communication, 1931.

Callus strength was clearly lower than normal during the first fifteen days of healing. Thereafter it varied less. The histologic appearance of the different fractures varied more than did the healing strength. We were unable to demonstrate histologically any decided reduction in the number of cartilage cells in the fractures. If callus strength was less than normal during the first fifteen days, when we have shown phosphatase to be at its height, it is conceivable that, owing to a reduction in the diet of the substances on which phosphatase acts, callus strength might be reduced, and this, in itself, may explain the early variations from normal.

If the lowered strength during the first fifteen days is due to a lack of salt in the diet, it should follow that the strength was more reduced on the low total salt diet than on either the low phosphorus or the low calcium diets. This proves to be the case, as we have reported elsewhere. Further, the strength of the callus in its early stages would be more reduced on the calcium than on the low phosphorus diet if the calcium salts are more closely concerned in the strength of the callus than are phosphorus salts. This also proves to be true.<sup>2</sup> In the histology of the fractures of the animals on the low calcium diets, we were struck by the absence of calcification as compared with that appearing in the animals on the other two diets, and although the healing strength was not extremely reduced in the animals on the low calcium diet, it was definitely less than that in those on the low phosphorus diet.

#### SUMMARY

A histologic study of healing fractured fibulae of rats on low total salt, low calcium and low phosphorus diets has been made. There is some evidence of correlation between the histology and the breaking strength of these calluses, but the correlation is not as complete as could be desired. It is believed that further evidence of an indirect nature is presented on the importance of phosphatase to the healing of bone.

## TUMORS OF THE SMALL INTESTINE

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BALTIMORE

The subject of neoplastic growths occurring in the small intestine is a difficult one to approach in view of the paucity of material. The infrequency of gastro-intestinal tumors located between the pylorus and the ileocecal valve is one of the many unsolved problems of cancer pathology and it is interesting to speculate why this part of the alimentary canal is relatively immune to tumor invasion when the portals of entrance and exit, namely the stomach and the large intestine, are among the most common sites for cancer. Literature on this subject is not scarce, but the majority of publications in the past have dealt with case reports alone. Few authors have ventured to discuss the theories of causation and pathogenesis. A former paper (1931) dealt with the clinical aspects of tumors of the small intestine, special emphasis being laid on the diagnostic importance of the roentgen rays. The purpose of this article is to summarize the cases recorded in this hospital and to discuss the occurrence, the clinical features and the histopathology of the group.

Interest in small intestinal growths was aroused by the occurrence of two cases in the wards of the Johns Hopkins Hospital during the past year. Since that time three cases have been reported from other hospitals in Baltimore. A search of all available material then revealed eighty-eight cases of tumors of the small intestine. This material included 11,500 autopsies in the general pathological department and 45,000 specimens from the surgical pathological department, a large percentage of the latter including specimens sent from other hospitals for diagnosis.

The frequency of tumors of the small intestine can best be appreciated by a comparison with tumors occurring in the rest of the gastro-intestinal tract. Tables 1 and 2 illustrate this relation. It will be noted that tumors of all types occurring in the small intestine comprised 8.9 per cent of all gastro-intestinal tumors. Those of benign character are relatively more frequent in the small intestine, comprising 23.8 per cent of all benign tumors. Malignant tumors are, comparatively speaking, less common, occurring in only 4.9 per cent of all those in the gastro-

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From the Surgical Pathological Laboratory of the Johns Hopkins Hospital and University.

intestinal tract. These values parallel closely figures quoted by other writers on the subject. Herman and von Glahn, considering malignant tumors alone, placed the incidence at 3.1 per cent. Ewing reported a value of 3 per cent; Forque and Chavin, reviewing 88,031 autopsies, placed the incidence at 6 per cent.

A thorough perusal of the literature yielded 339 tumors of the small intestine, the reports of which could be considered authentic. While

TABLE 1.—*Distribution of Nine Hundred and Eighty-Six Gastro-Intestinal Tumors*

Source		Cases From the Surgical Pathologic Department	Cases From the General Pathologic Department	Total
Stomach.....	Benign.....	0	58	58
	Malignant.....	263	190	453
Total.....				511
Colon and rectum	Benign.....	51	36	87
	Malignant.....	190	91	281
Total.....				368
Appendix.....	Benign.....	8	0	8
	Malignant.....	9	0	9
Total.....				17
Small intestine....	Benign.....	13	37	50
	Malignant.....	20	18	38
Total.....				88
Grand total.....				986

TABLE 2.—*Ratio of Tumors of the Small Intestine to Total Gastro-Intestinal Neoplasms*

All tumors		
Gastro-intestinal.....	986	
Small intestine.....	88	(8.9%)
Benign tumors		
Gastro-intestinal.....	210	
Small intestine.....	50	(23.8%)
Malignant tumors		
Gastro-intestinal.....	776	
Small intestine.....	38	(4.9%)

the number reported in the present series is relatively large, it must be remembered that all atypical growths, excluding infectious processes, were considered. The majority of these were asymptomatic and were recognized accidentally at autopsy.

The majority of writers have neglected to discuss the infrequency of this group of tumors from the etiologic standpoint, and while such neglect is perhaps justifiable in the present state of knowledge, there are certain characteristics in which the small bowel differs from the stomach and large intestine. These differences have to do with the



embryology, anatomy and physiology of this portion of the intestine, and therein may lie the basis of its insusceptibility to tumor invasion.

Summarized briefly, the small intestine is an epithelial-lined tube that has undergone rapid elongation in the embryo out of proportion to the rate of growth of the remainder of the gastro-intestinal tract. It is a coiled tube of relatively uniform size, the lining of which is characterized by villi between which lie the crypts of Lieberkuhn. The mucous glands of Brunner are found in the submucosa of the duodenum and upper jejunum, while the terminal ileum harbors collections of lymphoid tissue known as the agminate nodules or Peyer's patches. Food materials pass through the small intestine rapidly, with little or no stasis, save in the lower ileum. The absorptive power is greater in the small bowel than in any other portion of the intestinal tract, and it contributes the great majority of the secretions essential to

TABLE 3.—*Varieties and Location of Tumors of the Small Intestine*

Type	Duodenum	Jejunum	Ileum	Undetermined	Total
Carcinoma.....	7	4	3	2	16
Sarcoma.....	0	1	1	0	2
Lymphoblastoma.....	1	0	18	2	21
Adenoma.....	4	1	10	0	15
Myoma.....	0	1	2	0	3
Fibroma.....	1	0	3	0	4
Hemangioma.....	1	1	1	0	3
Chylangioma.....	0	1	0	0	1
Hematoma.....	0	0	1	1	2
Accessory pancreatic tissue.....	2	3	1	0	6
Argentaffin tumors.....	1	1	5	0	7
Lipoma.....	3	1	3	0	7
Cyst.....	1	0	0	0	1
Total.....	21	11	48	5	85

digestion in an alkaline medium. While it may seem impracticable to attempt to prove a relationship between these factors and the infrequency of neoplastic growth, they should receive due consideration.

The relative freedom from stasis of the small intestine should be regarded as significant. The terminal ileum is the only part of this field in which the fecal contents are brought to a standstill and accumulate before passing into the cecum. This is the region in which the tumors of this series are found to occur most frequently. Stasis likewise is found in the stomach and large intestine, and these sites are especially susceptible to tumor invasion. Stasis is known to be conducive to irritation, and if one accepts the irritation theory of the etiology of cancer, this must be accepted as a contributing factor.

The embryonic theory of Cohnheim has many supporters, and in certain cases it clearly accounts for tumor origin. If one bears in mind the fact that the small intestine develops chiefly during the latter four months of fetal life it is plausible to assume that there is far less opportunity for arrested development and misplaced embryonic tissue here than in the remainder of the gastro-intestinal tract.

The variety of tumors in this series and their distribution may be comprehended at a glance at table 3.

Tumors of the lymphoblastoma group, about which much confusion still exists and which will be taken up in detail later, were found to be most common, occurring in twenty-one instances. Eighteen were located in the ileum, the site of election being the terminal portion. Carcinomas were the next in frequency, accounting for sixteen of the

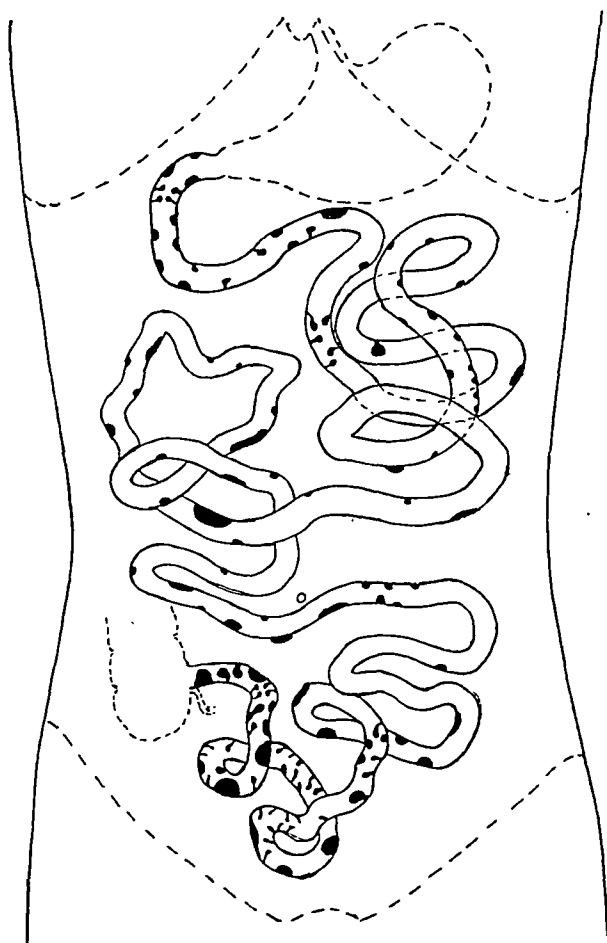


Fig. 1.—Diagrammatic representation of distribution of benign tumors throughout the small intestine. Note the smaller size, the predominance of the polypoid form and the greater frequency of localization in the lower ileum as compared with the malignant tumors in figure 2.

eighty-eight cases. The duodenum was most frequently involved, eight being located in that region, while the jejunum and ileum showed four and three, respectively. Adenomas were third in frequency, fifteen cases being found, eleven of which were located in the ileum. While these were the predominating types, attention should be called to the argentaffine group of tumors. Although these were formerly thought to occur only in the appendix, in this series seven were found in the small bowel,

five in the ileum and one in the duodenum. Lipomas, accessory pancreatic tissue and fibromas are among the other important benign tumors.

The distribution of the tumors throughout the small intestine is shown graphically in the accompanying diagrams. Figure 1 represents benign tumors, and figure 2, malignant. These are purely diagrammatic sketches for the purpose of showing the approximate locations and of

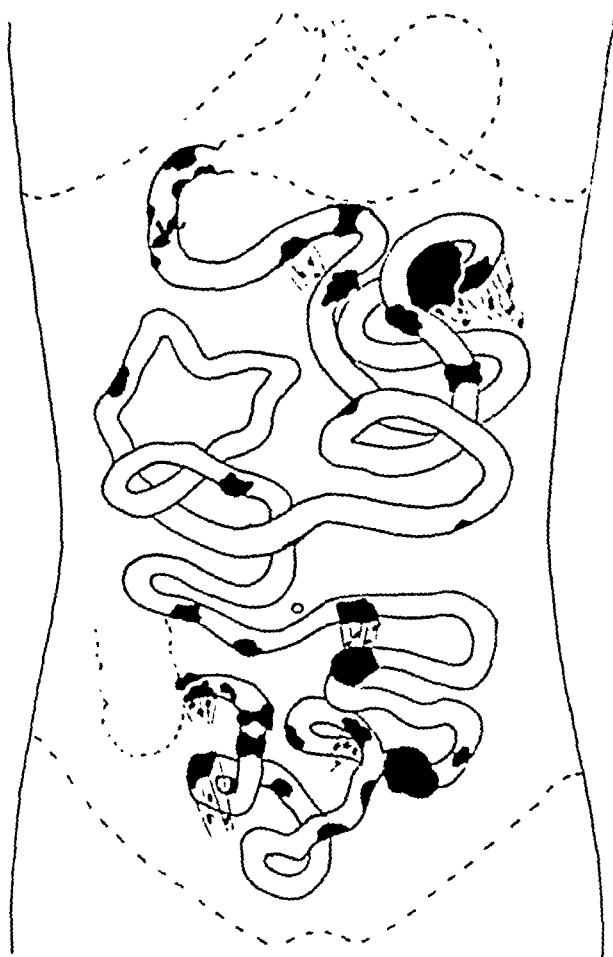


Fig. 2.—Diagrammatic representation of distribution of malignant tumors throughout the small intestine. Metastases are denoted by small dots in the lines radiating from the intestine. The tumors are larger and more invasive, and the points of election are the duodenum as well as the lower ileum. Compare with the distribution of benign tumors in figure 1.

contrasting the size of the gross tumors. Two features may be noticed at a glance. The terminal ileum is attacked much more frequently by both benign and malignant growths. The duodenum is next in susceptibility, whereas the jejunum is relatively free. The character of the growths is different in the two diagrams. Malignant tumors are larger, are usually single, and frequently show involvement of the glands or direct extension to the mesentery. Benign growths on the contrary, are smaller, often multiple and usually polypoid.

## GENERAL TYPES OF TUMOR GROWTH

The type of growth assumed by neoplasms in the small intestine is worthy of note at this point, since a general classification holds for all tumors regardless of their histologic class or state of malignancy. The simplest classification deals with the direction that the tumor assumes

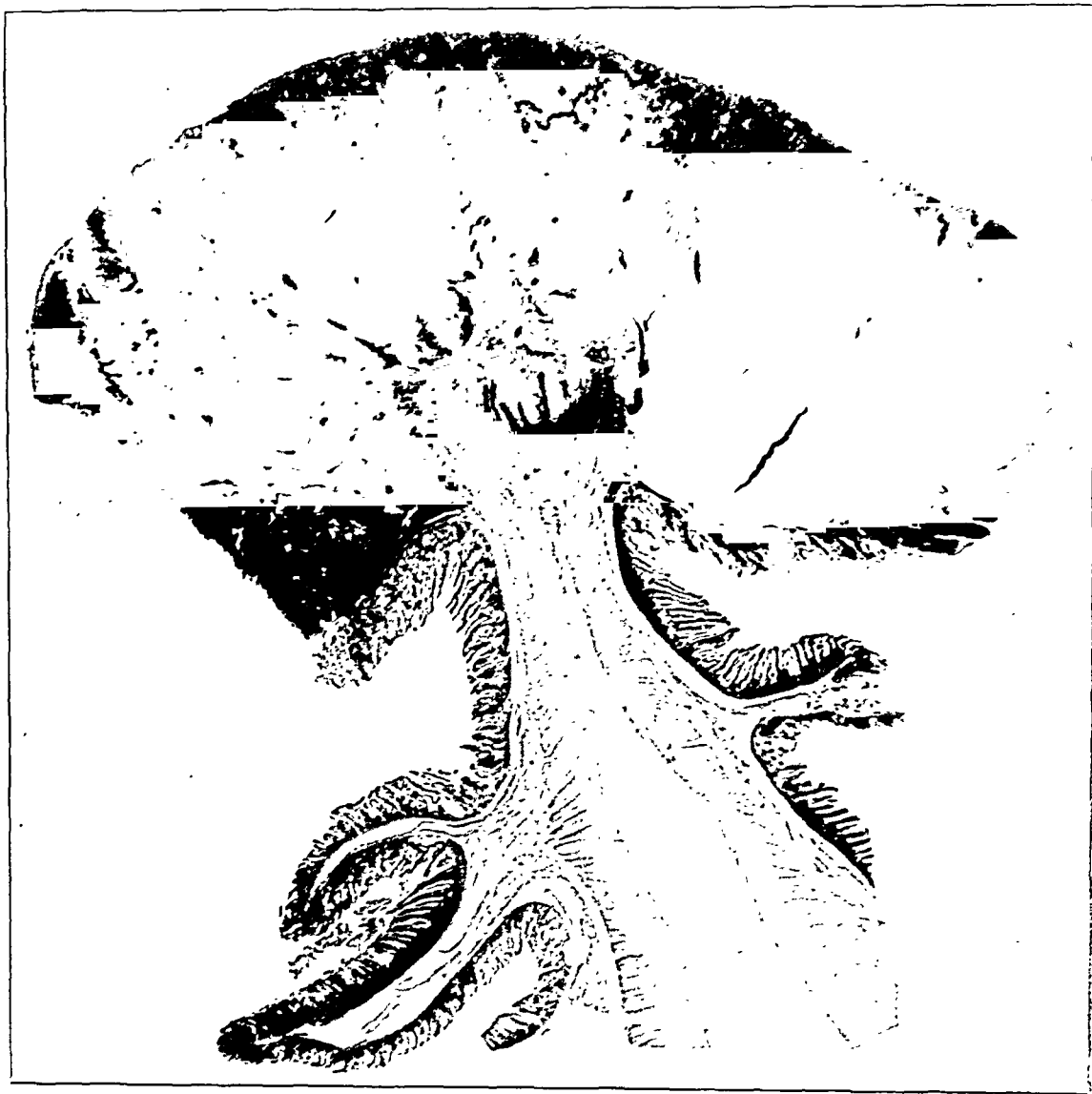


Fig. 3 (path. no. 16485).—Low power photomicrograph of the entire section through a lymphoblastoma of the ileum. This illustrates the polypoid type of tumor growth. The mucosa covered the base of the tumor and the pedicle, but was eroded from the surface.

in its growth, whether toward or away from the lumen of the intestine. Accordingly, they may be intraluminal or internal or, in contradistinction, extraluminal or external.

The external type (see fig. 14) is comparatively rare, occurring in only 5 per cent of this series. The determining factors are evidently two: the source of origin and the mechanical condition of free space. Growths originating in the outer layers of the intestinal wall find less resistance offered by the serosa than by the rest of the wall, unless the intestine at that point lies in proximity to an unyielding viscus. Malignant tumors with a predisposition to extension usually grow out into and along the mesentery and are consequently predominant among the external tumors.

The vast majority of intestinal tumors, especially the benign, assume the internal form, probably for reasons the converse of the foregoing. They commonly arise from the internal layers of the intestine where

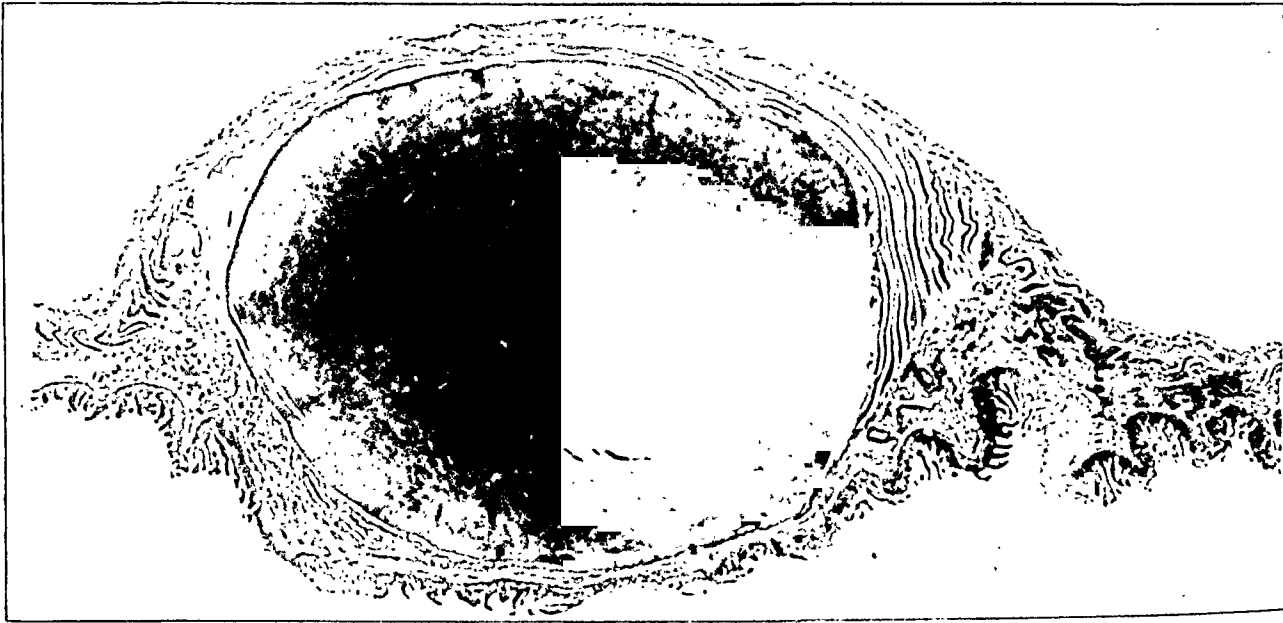


Fig. 4 (path. no. G10584, case 6).—Low power photomicrograph of the entire section through a myoma of the ileum. This illustrates the sessile type of tumor growth. The tumor arose from the circular layer of the muscularis. It was encapsulated and had pushed the normal submucosa and mucosa inward while forcing outward the longitudinal muscular layer and the serosa.

inward resistance is weakest. This type of tumor varies widely in form, but may be roughly classified as polypoid, sessile or extensive.

Polypoid tumors (fig. 3) are commonly benign, although it is not unusual to find in them secondary malignant change. They comprise the large group to which the diagnosis of intestinal polyp is often carelessly given. This term is loosely used by some pathologists as a final diagnosis, but while the majority are adenomas, almost any histologic type may assume the form of a polyp. They originate as small infoldings of mucosa into which the submucosa herniates, together with the tumor cells. The passing intestinal contents exert a constant force,

pulling and drawing on the base until a pedicle is formed, which may vary in thickness from a tiny thread to a thick cord 1 cm. or more in diameter, and in length from a few millimeters to 3 or 4 cm. This is the form of tumor that is often responsible for intussusception. Polyps rarely attain a size larger than that of a walnut before they are recognized by symptoms of obstruction. Multiple polyposis is not an infrequent occurrence.

Sessile tumors (fig. 4) are oval or round tumors of varying thickness. They may lie within the wall of the intestine and be classed as

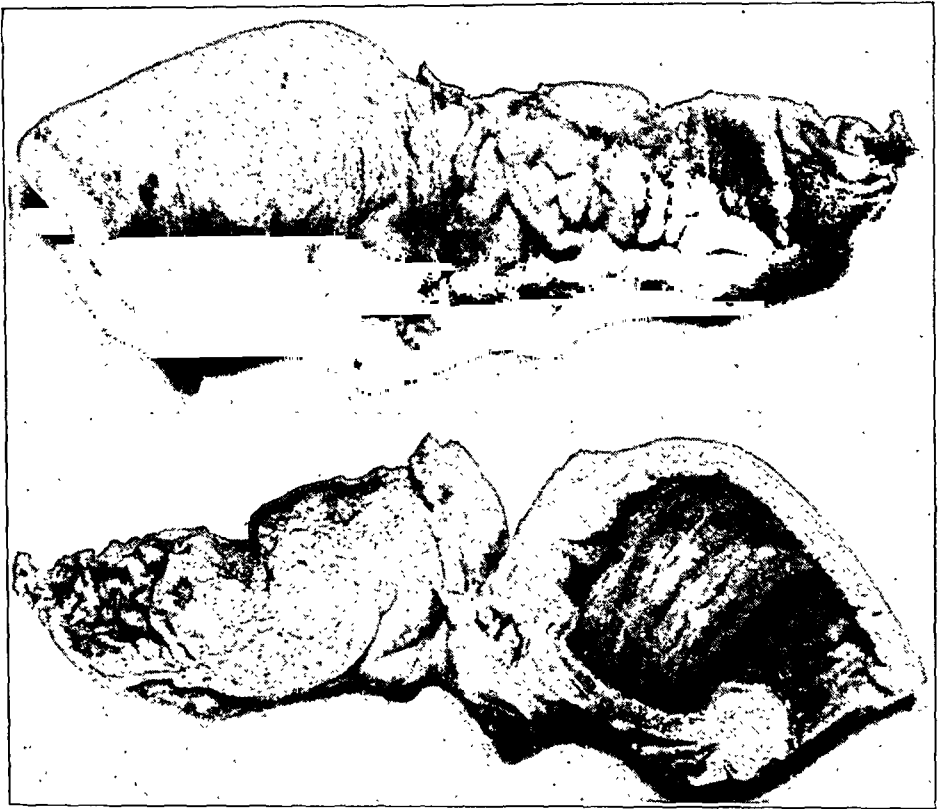


Fig. 5 (path. no. 26163).—Gross specimen of a lymphoblastoma of the ileum. The lumen was almost completely blocked by a constricting growth. There was marked thickening and induration of the walls on either side of the constriction caused by infiltration of the tumor. Note the dilatation of the proximal and the collapse of the distal portions of the lumen. This represents the constriction type of tumor growth.

intramural, or they may be attached to the wall by a broad base. In either event, they are usually covered loosely by mucous membrane. Undoubtedly, they may become polypoid under the influence of the conditions described in the preceding paragraph. This form is usually assumed by benign tumors, but malignant tumors may be sessile before the process of invasion has extended to the surrounding tissues. The mucous membrane is intact, unless it is eroded by constant pressure of intestinal contents.

Infiltrative growth is used to designate the tumors, usually malignant, that originate in the wall and extend rapidly either around the lumen or in a longitudinal direction. They produce a jagged, irregular thickening, spreading out from the site of origin, blasting away the normal structure and eroding the mucous membrane.

The constricting type of tumor (fig. 5) is a variant of the preceding form, but is so definite and frequent as to deserve separate consideration. It is the result of a malignant infiltrating growth that encircles the lumen of the intestine, producing a constriction that in some instances is so great that a tiny distorted tubule is all that remains of the former lumen. This form of growth occurs with surprising frequency in the lymphoblastomas and may prove of some value in predicting the state of malignancy in this obscure group. Some of these tumors show a striking tendency to necrosis and excavation, so that the tumor remains a hollow irregular sphere through which the lumen passes, constricted at its points of entrance and exit. The center may become necrotic, and is often diagnosed as an abscess at operation and its true nature revealed only by frozen section.

#### PATHOLOGIC DATA

The pathologic study of this group of tumors is facilitated by dividing them into groups according to their malignancy. The malignant tumors include carcinomas and sarcomas. Lymphoblastomas constitute a borderline group and are considered separately. The remainder fall into the benign class and are composed of adenomas, fibromas, myomas, lipomas, argentaffin or carcinoid tumors, accessory pancreatic rests and angiomas. Enterocysts, cystic pneumatosis and neuroblastomas comprise a rare group of little clinical significance. Further subdivision of these groups will be made in order.

#### MALIGNANT TUMORS

##### CARCINOMAS

The literature on carcinomas is the most abundant, and many figures have been quoted regarding the relative occurrence. This is due not to the prevalence of this tumor so much as to the greater interest it has aroused. The incidence quoted by various writers varies somewhat, but it is generally agreed that carcinomas of the small intestine compose between 3 and 10 per cent of all gastro-intestinal carcinomas. This value was found to be 4.9 per cent in this series. Analysis of the 11,500 autopsy specimens from the general pathologic department yielded six cases, or 0.05 per cent. Carcinomas comprised 18.1 per cent of the eighty-eight tumors of this series.

Persons of "cancer age," or those in the fifth and sixth decades of life, are most susceptible to carcinoma of the small intestine. The

average age in sixteen cases was found to be 52. The oldest patient was 68 and the youngest 33 years. The male sex is most susceptible, being affected in eleven instances. No reason is known for the difference in incidence in men and women, but it agrees with the figures for carcinomas elsewhere in the intestinal tract. The disease occurs twice as often in the white race as in the colored. This variation, however, is coincident roughly with the ratio of the two races coming under hospital observation.



Fig. 6 (path. no. 26196, case 1).—Photograph of the gross specimen of an annular carcinoma of the jejunum. The tumor had produced almost total obstruction of the lumen, with proximal dilatation and distal collapse of the intestine. Note the persistence of the valvulae conniventes after dilatation.

Carcinoma is found more frequently in the duodenum than in any other portion of the small intestine in spite of its abbreviated length. This predominance is sufficient, even in this limited number of cases, to justify the conclusion beyond that of an accidental finding. Johnson disagreed, stating that if the papilla of Vater is excluded, carcinoma of the duodenum is almost unheard of. Clark agreed that the duo-



denum is most frequently attacked, and Vickers stated that carcinoma occurs in that location as often as in the rest of the small intestines combined. Although not borne out in this series of cases, the next susceptible site is commonly regarded to be the terminal ileum, while the remainder of the ileum and jejunum are infrequently the seat of malignant growth. Further subdivision of the duodenum is necessary to demonstrate the distribution of carcinomas. It is generally conceded that the second or periampullary region is most frequently invaded, and such was the case in seven tumors of this group. Three were located in the middle third, two of which involved the ampulla, two involved the first third, and two the terminal third.

Metastasis to other organs is the criterion *par excellence* for the estimation of malignancy and was found in four, or 25 per cent. of the



Fig. 7 (path. no. 44556).—Photograph of the gross specimen of an adenocarcinoma of the duodenum removed at autopsy. The tumor occupied one side of the intestinal wall and the edges were raised and curled over the ragged, ulcerated base. The lumen was blocked by encroachment of the tumor, and the patient died of intestinal obstruction. (Material obtained through courtesy of the Baltimore City Hospital).

cases. This is not as high as the incidence given by Craig or Clark, nor as frequent as metastasis from carcinoma of the stomach. The latter fact is explained by the earlier recognition of the condition in the small intestine. The first site of metastasis is the mesenteric glands. The next in order are the peritoneum, the liver and the lungs, but extension beyond the mesenteric lymph glands is rare.

The gross forms assumed by carcinomas of the small intestine may be grouped roughly in order of their frequency as follows: The constricting or stenosing form (fig. 6), the infiltrating ulcerative type (fig. 7) and the polypoid form (fig. 13). The size is exceedingly

variable. The smallest in this series were tiny submucous nodules a few millimeters in diameter, which appeared benign until the histologic sections were examined. The largest was the size of a grapefruit, infiltrating, ramifying and involving the surrounding structures. Those of the external type are rare, but attain the largest size in view of the fact that they do not cause early symptoms. The polypoid tumors rarely grow larger than a hen's egg before symptoms of obstruction reveal the presence of a pathologic condition. The color is pearly white, and the consistency is firm and hard. The mucous membrane may be intact over the early growth, but in the older infiltrative form, the mucosa is usually eroded, and a ragged ulcerated area designates the inner surface of the tumor. The tumor cuts almost like cartilage, is bluish white and looks fibrous.

Four main types of carcinoma occur in the gastro-intestinal tract: adenocarcinoma, medullary, scirrhus and colloid, as differentiated by their histologic characteristics. The first is by far the most common, the second much less frequent, and the last two very rare.

The term adenocarcinoma is used to designate tumors the cells of which have a tendency to retain their original glandular formation. They arise from the epithelial cells of the mucous membrane and grow rapidly into the wall of the intestine in sheets and strands, displacing the normal structural elements and forming typical glandular nests of cells. This glandular formation is so perfect, in fact, that the tumor could easily be mistaken for a benign glandular hypertrophy were it not for the cellular mitoses and extensive invasion characteristic of malignant tumors. The cells are commonly of the tall columnar variety, but may be cuboidal or even stratified. There is a moderate amount of pink-staining cytoplasm, at the base or middle of which lies the large, oval, hyperchromatic nucleus. Mitotic figures are abundant. While the cells remain in a more or less orderly arrangement about the acinus, these cell groups are scattered through the underlying tissue with utter disregard for the normal cellular structure, leaving the harassed fibrous and muscular tissue as a weakly ineffective supporting stroma. The mucosa covering the tumor is often the seat of erosion and secondary infection. One finds a sudden break in the normal mucous membrane under which the tissue is partially degenerated and harbors a dense cellular infiltration.

Adenocarcinomas do not always retain the pure glandular form described. The new cells apparently have little regard for the parent growth, and, after beginning the march of invasion, form sheets and nests of cells that bear only a rough resemblance to true acinar formation. The cells are round, irregular or cuboid, and are packed closely together. The cytoplasm is moderate in amount, and the nuclei are vesicular, vary in size and staining reaction and usually show mitosis.



Fig. 8 (path. no. 26196, case 1).—Low power photomicrograph of an adenocarcinoma of the jejunum. The tumor cells can be seen arising from the depths of the crypts and extending into and through the submucosa and muscularis. The alveolar arrangement of the cells is roughly preserved.

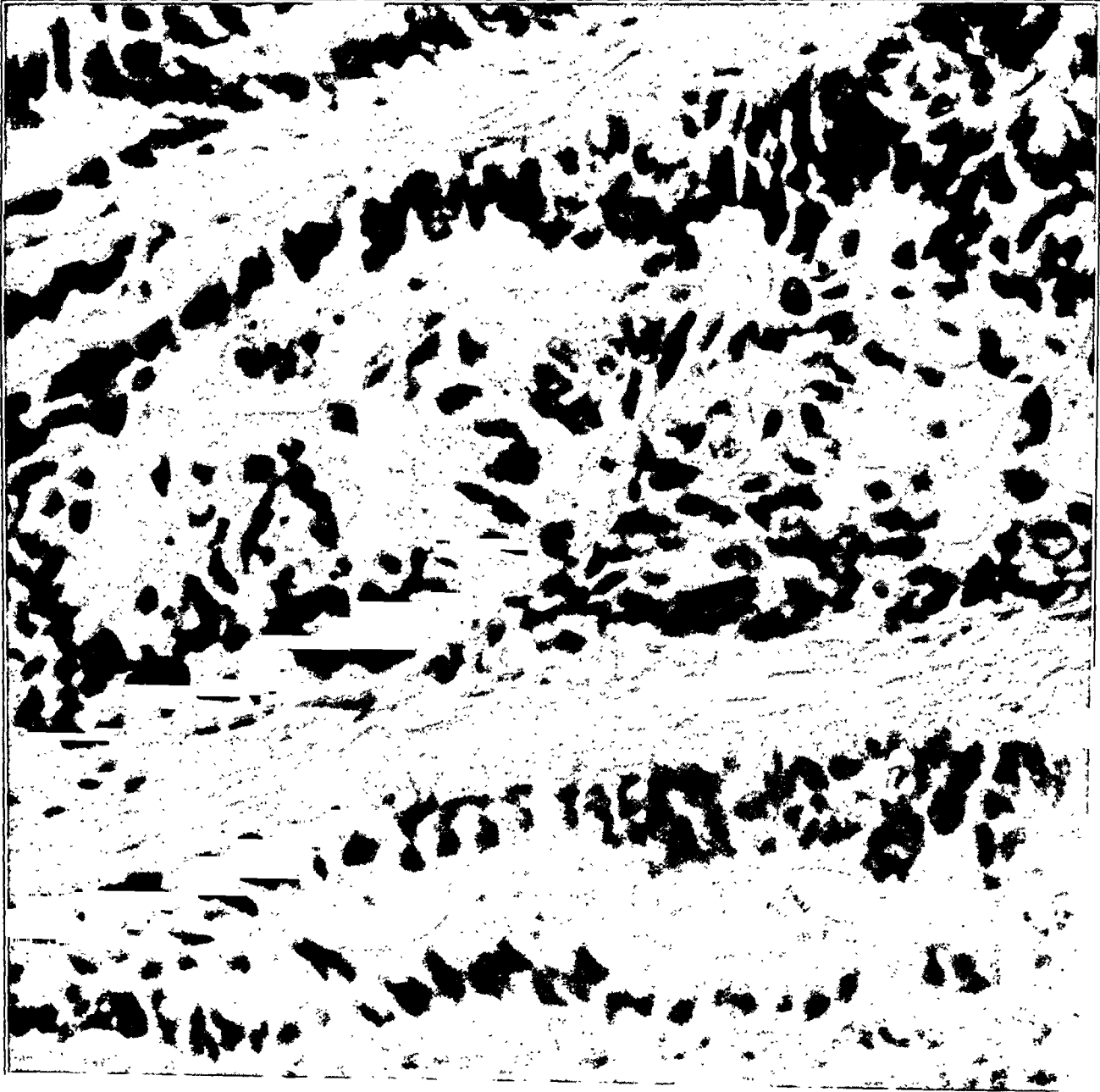


Fig. 9 (path. no. 26196, case 1).—Higher magnification of the tumor shown in figure 8. The photograph was taken through the lower part of the crypts. Note the atypical arrangement of the cells. The columnar shape has disappeared, and the cells lining the crypts are several layers deep. Some of the nuclei show mitoses.

The medullary type of carcinoma is softer and more spongy than the preceding type. It forms a fungating mass which bleeds easily. The cells are derived from the epithelial cells of the mucosa, but show no tendency to reproduce the glandular formation. This type of tumor



Fig. 10 (path. no. 26196, case 1).—Low power photomicrograph of a section taken from a lymph node in the vicinity of the tumor shown in figures 6, 8 and 9. The metastatic cells retained the property of alveolar formation. The steps of the reproduction can be followed in the upper right corner of the photograph. The individual cells are usually in a single layer, but are irregular in size. The columnar shape has been entirely lost.

is very malignant and spreads from the site of origin, recognizing no impediment to its progress. The cells form solid sheets and strands. They are closely packed, bearing a slight resemblance to squamous cell carcinoma. The cytoplasm is scant and takes a light eosin stain.

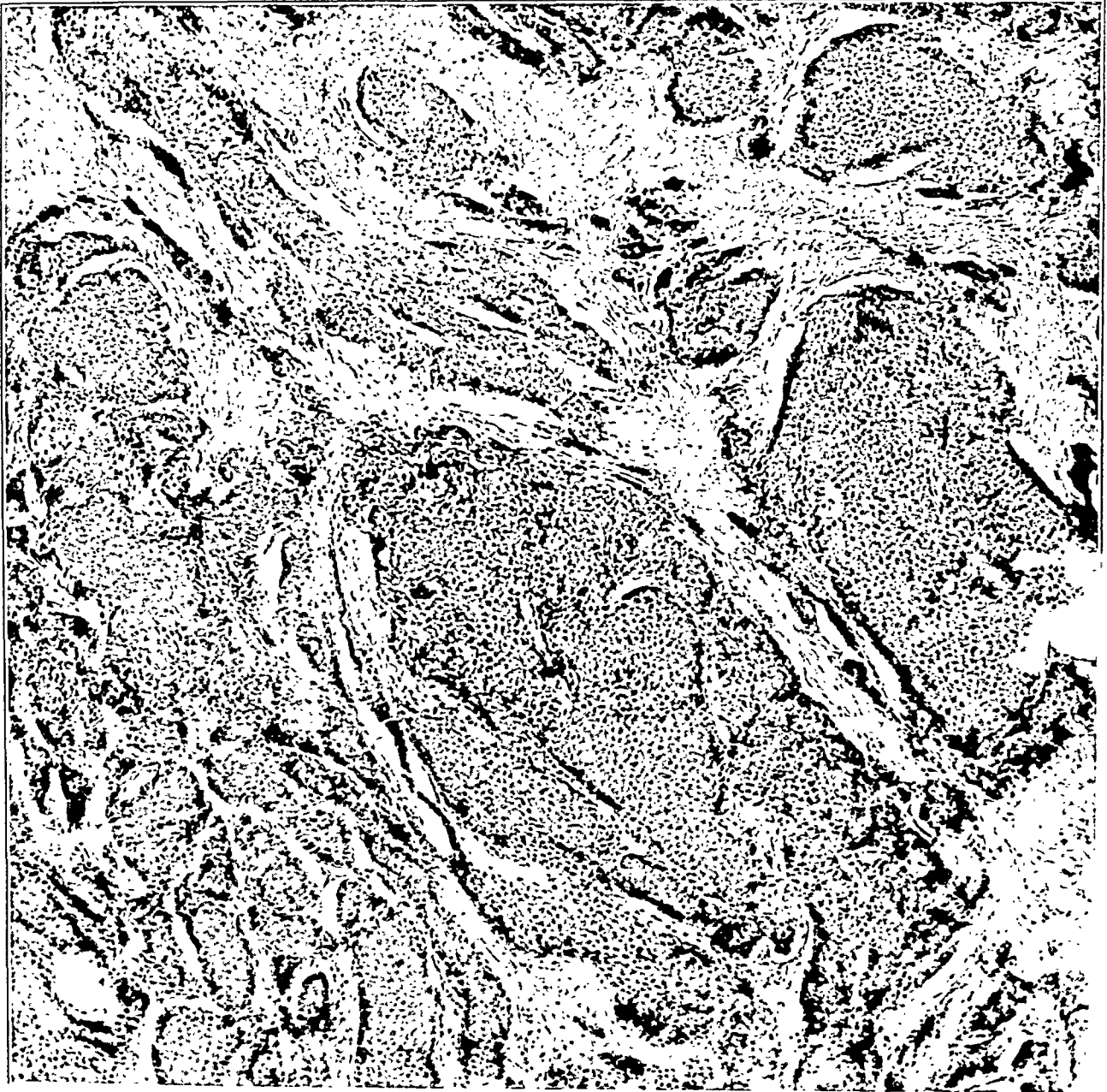


Fig. 11 (path. no. 31805).—Low power photomicrograph of a medullary carcinoma of the jejunum, metastasizing to the aortic glands. The cells are seen in solid strands and sheets invading the entire intestinal wall. Higher magnification showed a marked similarity between these cells and those of a squamous cell carcinoma. The cytoplasm is abundant, and mitoses are common.

The nucleus is large and light-staining, but contains numerous hyperchromatic particles. The submucosa and muscularis have either retracted before the advancing tumor edge or have been caught between the sheets of cells and compressed to narrow bands. Metastasis to glands takes place early, and the same situation is found. All of the normal glandular structure has either been replaced or pushed aside to make room for the metastatic cells.

Colloid carcinoma is very rare in the small intestine, but when it does occur, it assumes a form almost similar to the same type of tumor in the stomach, where it is not an infrequent invader. The tumor is largely external and consists of a lobulated gelatinous growth, fluctuant to the touch. The cut section shows a cystlike structure, the spaces of which are filled with a semisolid material that can be squeezed out. It represents a degenerate mucoid form of adenocarcinoma, according to Horsley.

It presents a characteristic histologic picture. According to MacCallum, two distinct types are found. The first is composed of cystlike cavities lined by a single layer of epithelium and filled with a glairy mucoid fluid. In the second type the cavities contain, besides the fluid, free tumor cells, each containing a drop of the same glairy fluid, which displaces the nucleus to one side and causes it to resemble the signet ring cell of Krompecher.

The pathogenesis of carcinomas in the small intestine is no less obscure than that of tumors elsewhere in the body. Certain facts have become established regarding their origin and manner of growth that may be considered authentic. Dewis and Morse stated that the intestine offers three possible points of origin. The epithelial cells of the mucous membrane give rise to the most common type, adenocarcinoma. A different type of glandular growth, which is less malignant, has been found to arise from the glands of Brunner in the duodenum. Aberrant pancreatic rests have been considered as a third source, but, since they are relatively rare, malignant change in them is of little importance.

The question of a malignant condition arising in a preexisting ulcer is still a mooted one. Although pathologists at large have not accepted this theory, the argument of MacCarty is convincing. Cases were found in this series that showed malignancy in the presence of an ulcer, but proof of the relationship is lacking.

Malignant change in an adenomatous intestinal polyp has received much consideration during recent years. Bordenhauer, Quinn and Landel first described the appearance of small areas of malignancy in an apparently benign adenoma. Subsequent treatises have supported the theory, until such malignant change is now recognized as a significant step in the histopathology of intestinal carcinomas. Tuttle claimed to have found evidence of malignancy in 75 per cent of his cases, while



Lockhart and Meisnery went so far as to predict ultimate malignant degeneration in all adenomas. Such a statement lacks supporting evidence and cannot be accepted at the present time. The presence of

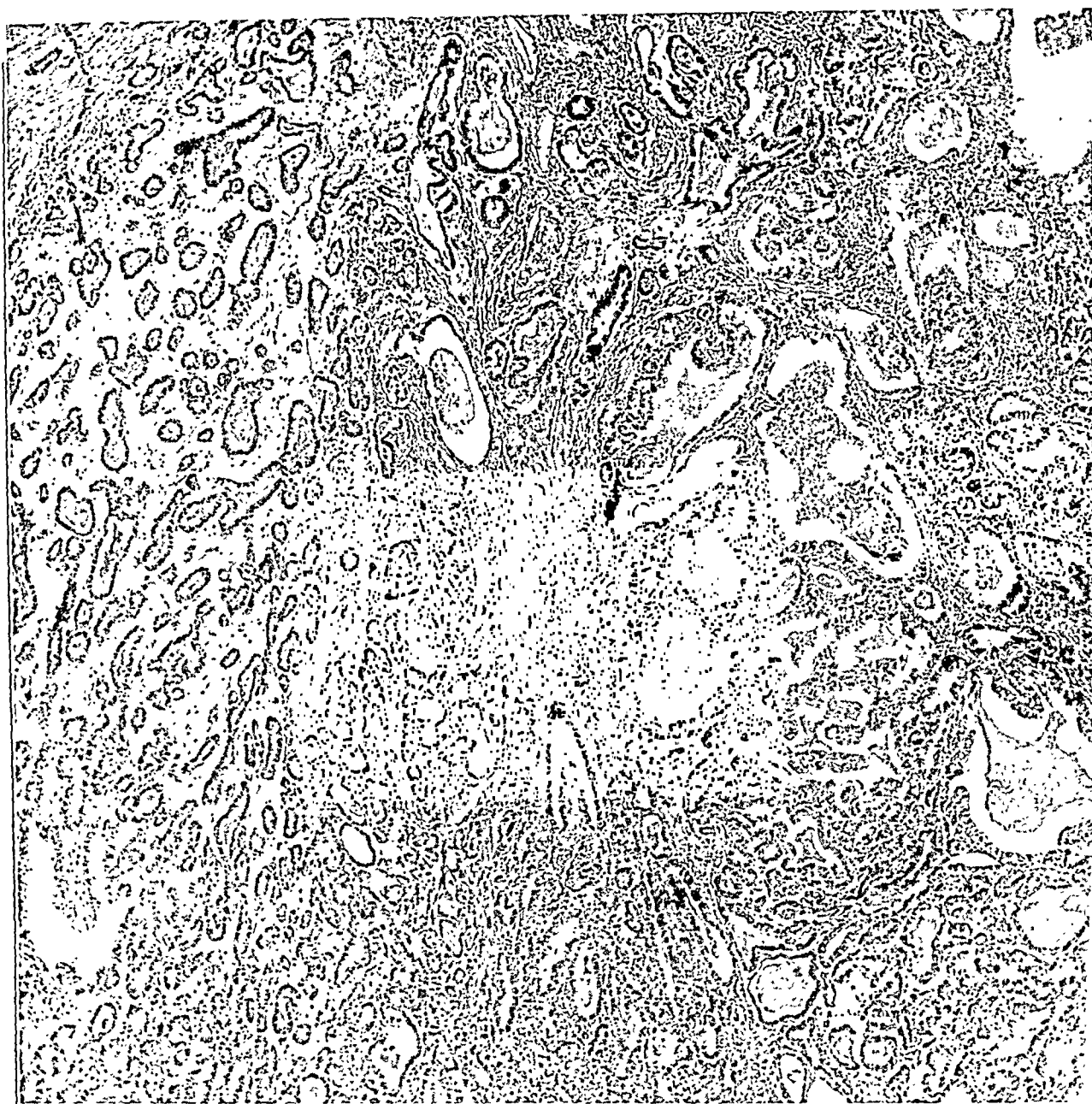


Fig. 12 (path. no. 46597).—Low power magnification of a papilloma of the duodenum undergoing malignant change. The cells composing the glands in the left and lower parts of the photograph are benign. In the right center, the glands are becoming dilated, and the cells are larger and more irregular. Mitotic figures were revealed by higher magnification (case of Dr. J. M. T. Finney).

malignant looking cells in an area of adenomatous hypertrophy is not sufficient to support the diagnosis of a malignant condition. At least



two conditions must be fulfilled; there must be definitely cancer cells, large, irregular and with mitoses, together with invasion of the basement membrane. The presence of metastases in advanced cases of course makes the diagnosis certain. Malignant degeneration is not, as the name implies, a degenerative process in which preexisting normal cells are converted into cancer cells. Carcinoma cells are self-propagative, and, once they have become established, an entirely new tumor growth follows. The adenoma may be considered as hypertrophied normal mucosa which is subject to invasion by carcinoma, just as the normal epithelial lining is, but which, through an abnormal arrangement, has been made more susceptible. Consequently, the typical picture of this condition is that of a benign polyp toward the edges of which areas of typical adenocarcinoma have arisen. These may have



Fig. 13 (path. no. 46597).—Gross specimen of the tumor shown in figure 12. The tumor arose from the duodenal wall just distal to the pylorus, and formed a fungating mass projecting into the lumen. Partial gastrectomy was performed, but the patient died of secondary infection of the abdominal wound and septicemia (case of Dr. J. M. T. Finney).

grown inward, pushing aside the benign portion of the polyp, but they more commonly grow outward as fungating masses of tumor. Such a tumor, showing malignant change, is shown in figures 12 and 13.

The mechanism of glandular reproduction in the growth of adenocarcinoma is an interesting pathogenic feature. This seems to be an inherent tendency of the mucosal cells. The youngest cells of the growth, found at the advancing edge of the tumor, do not show a glandular arrangement. This is also demonstrated in metastases to glands. The earliest invading cells are grouped in solid strands and nests. As growth progresses, they tend to arrange themselves in a circular fashion. The nuclei then retreat to the part of the cell farthest

from the center; vacuolation appears in the dentral ends of the cytoplasm, and finally this gives way, forming a hollow ring. These cells at no time show the typical columnar shape found in the parent epithelium. This process is admirably illustrated in figure 10.

The prognosis in cases of carcinoma is far from encouraging. If metastases have occurred, the ultimate result is uniformly fatal, and little can be done for the patient except the institution of palliative treatment. Fourteen of the sixteen patients in this series are known to be dead, and follow-up reports on the remaining two were unavailable. Even in the cases without apparent metastases, the patient usually succumbs to a recurrence of the tumor after removal.

#### SARCOMAS

The small intestine is the seat of tumors of mesoblastic origin in rare instances. The types commonly found are pure or variant forms of fibrous or spindle cell sarcoma, and are roughly the same as those found to occur in the stomach and large intestine. Among the miscellaneous types are included mixed forms, such as myxosarcoma and myosarcoma. The large group known as the lymphoid group of tumors may or may not be true sarcoma. They have been the subject of much discussion, and since their true nature is still obscure they are considered separately as a borderline group.

True sarcoma is rare in the small intestine as well as in the rest of the gastro-intestinal tract. Telling reported a spindle cell sarcoma in a child of 3 years, and Libman reported, in 1900, a case of similar nature in a white man of 42 years. Two cases are reported in this series, one of the spindle cell variety and the other a myosarcoma. Both patients were in the fifth decade of life. It is impossible to draw conclusions as to sex and race preferences in so small a number of cases.

The ileum is the site of election for sarcoma. Although one of the two cases was located in the jejunum, the other, with those reported in the literature, arose in the ileum. These sarcomas do not metastasize as readily as carcinomas. When metastasis does occur, the mesenteric glands are most frequently involved first, after which secondary invasion may reach the liver or lungs.

Sarcomas tend to assume the external type, growing out into the mesentery rather than into the lumen (fig. 14). The gross form is usually rounded, lobulated and encapsulated, in contrast to the finger-like ramifications found in the advancing border of a carcinoma. Early tumors are usually hard and elastic. In the more advanced stages they may have a soft spongy feeling, if central necrosis has occurred. The cut section is white and translucent. The size is variable, but often attains that of a child's head. One of the tumors in a case reported

in this series was as large as a grapefruit, around which the lumen of the jejunum stretched as a flattened tube.

Low power microscopic examination of a fibrosarcoma reveals the tumor to be composed of whorls and solid strands of connective tissue cells. Higher magnification shows typical spindle-shaped cells of fibrous connective tissue. They have a moderate amount of light-staining cytoplasm, in the center of which is located an elongated nucleus which also stains lightly, but shows numerous chromatin particles. These

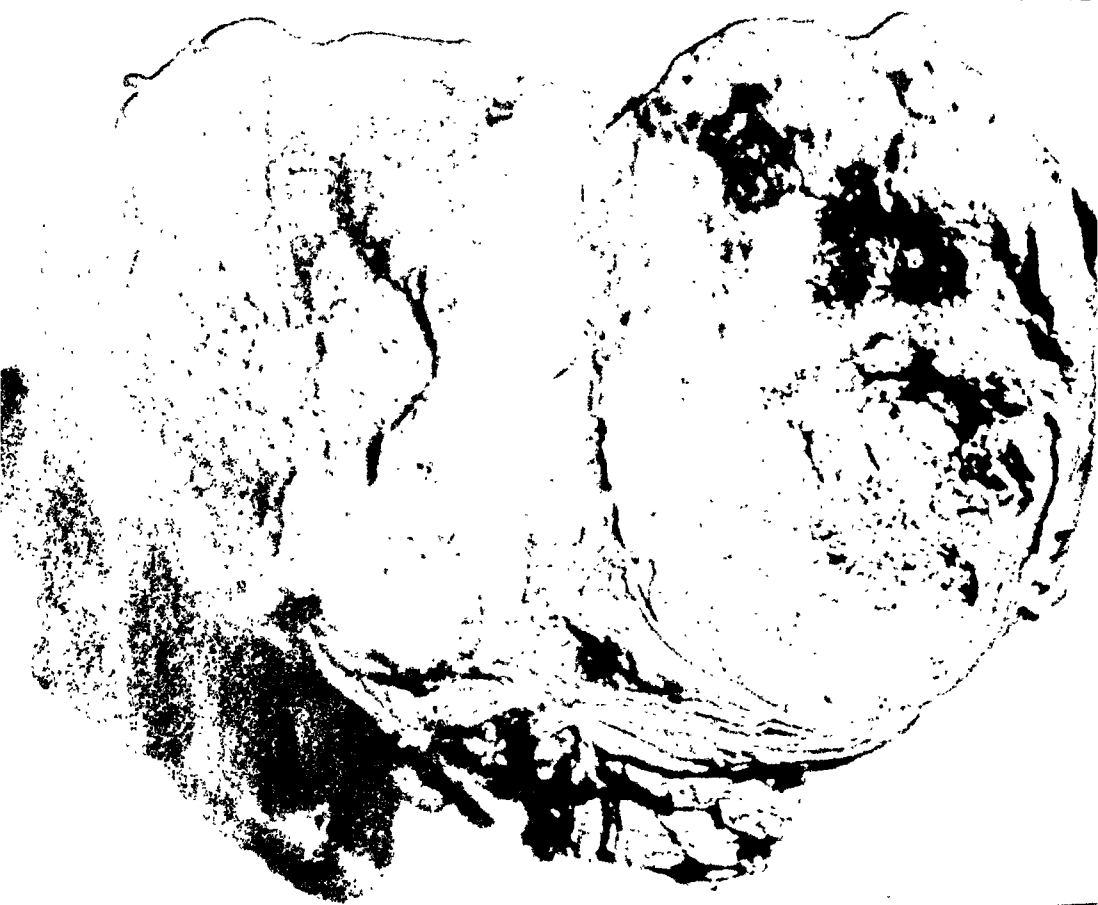


Fig. 14 (path. no. 44558, case 2).—Gross specimen of a large spindle cell sarcoma of the upper jejunum. The flattened lumen of the intestine can be seen encircling the lower part of the tumor. Note the central necrosis. The tumor arose from the jejunal wall and grew outward into the mesentery. Metastases had occurred in the liver. When first seen, the condition was judged inoperable, and the patient was treated palliatively. Specimen removed at autopsy (material obtained through the courtesy of Dr. MacCallum).

cells may be mistaken for round cells in some part of the section but this is due to the fact that the cells are here cut in coronal section. Fibroblasts are not infrequent, and are found in great abundance near the younger part of the tumor at the advancing edge. The most inter-

esting feature of sarcoma in general and one of the best criteria of malignant change is the total disregard that the cells seem to hold for the vascular system. They invade the smaller capillaries and arterioles, and in many instances may be found to occupy the lumen of the vessel.

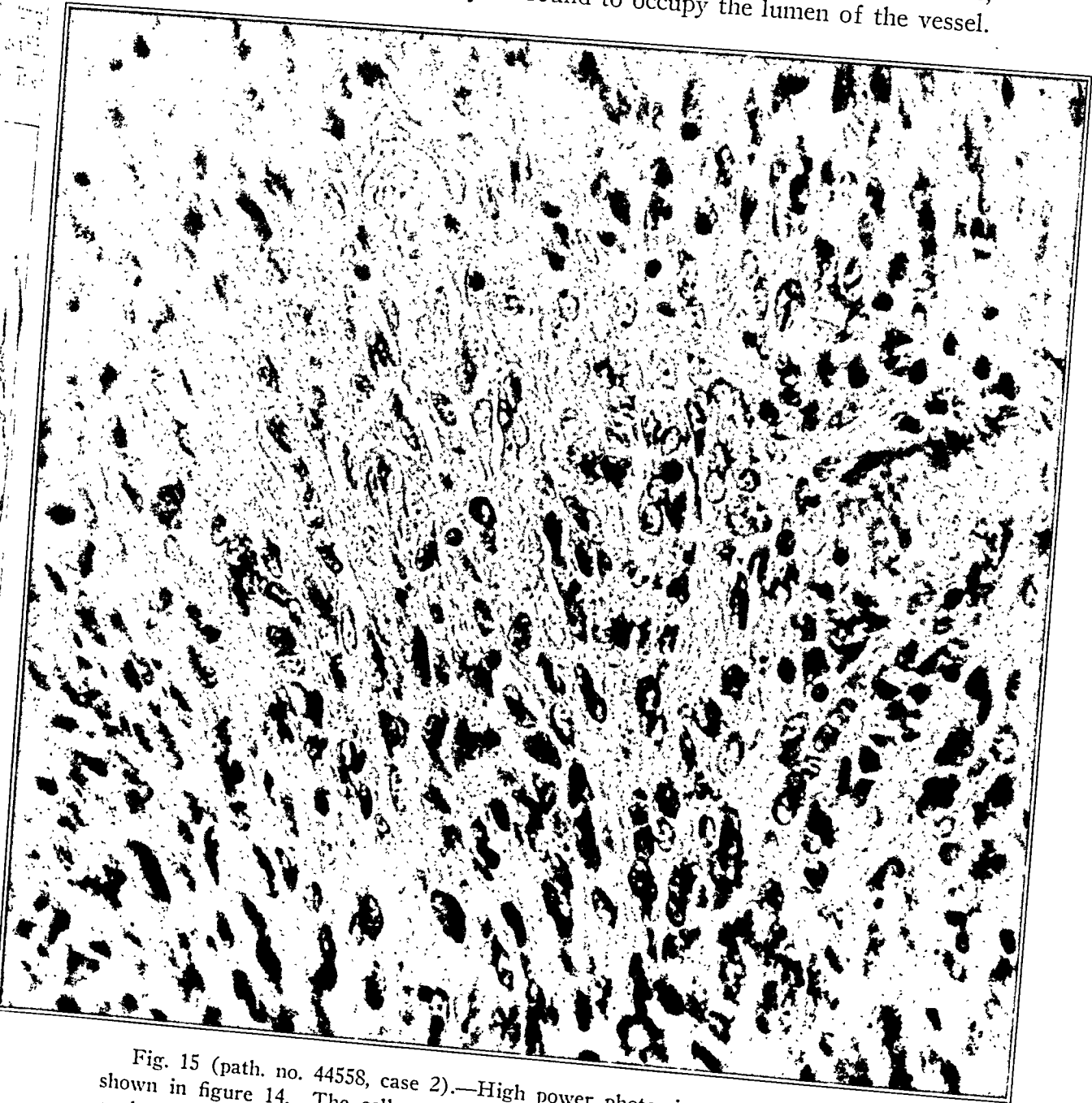


Fig. 15 (path. no. 44558, case 2).—High power photomicrograph of the tumor shown in figure 14. The cells are long and spindle-shaped and contain a large oval nucleus, in which mitotic figures can be seen. Note the beginning invasion of the capillary wall by tumor cells. Occasional fibroblasts can be seen.

A moderate cellular infiltration is present in almost every case. This consists of cells of the lymphocytic and myelocytic series and is greatest

when secondary infection has taken place. Vascularity is more marked than in carcinomas, and numerous capillaries can be seen throughout the tumor.

Myosarcoma presents an almost identical picture and is often confused with the spindle cell variety of fibrosarcoma. The cells arise from muscle tissue, however, and, although atypical, they retain certain characteristics that serve to distinguish them. The cytoplasm stains brighter pink with eosin, is thicker and more plump than that of fibrosarcoma. The nucleus is larger, hyperchromatic and shows many mitotic figures. One gains the impression, in fact, that the nuclei compose the essential part of the picture, and that the cytoplasm is crowded in as a supporting stroma. The tumor growth can usually be traced to an origin in the muscular coats of the intestinal wall. This type of sarcoma is not as vascular as the spindle cell variety, but shows the same tendency toward invasion of the blood vessels.

Myxosarcoma is popularly considered to be a degenerate form of spindle cell sarcoma and should not be confused with the pure form of myxoma found in other organs and thought to be of neurogenic origin. One finds, on examination, light areas scattered between strands of spindle cells. These areas show a faintly granular basophilic cytoplasm divided by isolated spindle and star-shaped cells. The matrix of these cells varies greatly in amount, but is apt to be grouped around blood and lymph vessels. Vascularity is marked, and the capillaries stand out prominently in the myxomatous area.

The pathogenesis of this group of tumors is fairly clear, but little can be said regarding the etiology. Sarcomas arise as abnormal proliferations of cells from any tissue of mesenchymal origin. These tissues in the small intestine are the connective tissue of the submucosa and subserosa and the smooth muscle tissue of the muscularis; hence the two types, fibrosarcoma and myosarcoma. Myxosarcoma, as just described, does not constitute a separate pathologic entity. The name is purely descriptive and is often used in the combined form.

Very little can be said regarding the etiology of these types of sarcoma. Nothnagel has suggested a chronic infectious process as being contributory. His discussion, however, included the lymphoblastomas, and probably does not apply to the pure types of sarcoma.

Sarcomas of these types give a better prognosis than carcinomas, for the reason that metastasis occurs less freely. The tumors grow more slowly and do not tend to break away from the circumscribed form early in growth. When recognized early and excised, the tumor does not tend to recur, and the patient may recover entirely.

#### LYMPHOBLASTOMAS

There is no group of neoplasms about which more confusion of nomenclature and classification exists than the lymphoid tumors of

the small intestine. They have been discussed in the literature under a variety of names, a few of which are lymphosarcoma, round cell sarcoma, lymphocytoma, chronic inflammatory tumors, Hodgkin's disease, pseudoleukemic granuloma, lymphoid granuloma and many others.

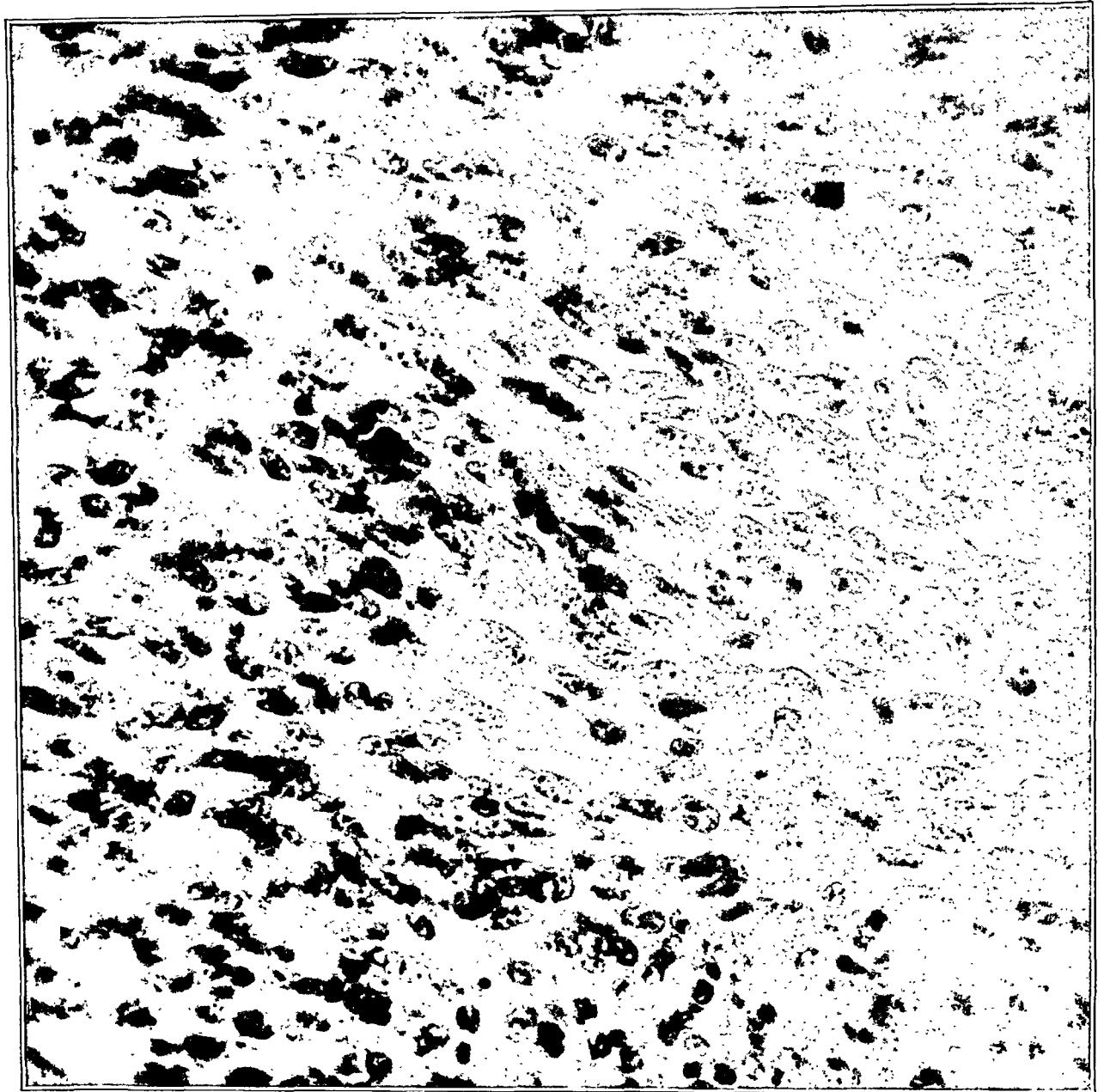


Fig. 16 (path. no. 37600).—High power photomicrograph of a myosarcoma of the ileum. The tumor caused no symptoms, but was found accidentally during operation for a ruptured appendix. The cells are large, contain a moderate amount of cytoplasm and large, plump, elongated nuclei with abundant mitoses. The origin of the tumor could be traced to the circular layer of the muscularis.

They have undoubtedly been known and recognized under some of these terms for many years. Baltzer, in 1873, noted their frequency in the

small bowel and reviewed a number of cases, classing them as sarcomas. Libman reported four cases in 1900 as lymphosarcomas. Crowther gathered 122 cases from the literature in 1913, and again in 1919 Graves extended the list to include 249. The latter noted the confusion surrounding a suitable classification and asked that all such tumors be included under the general term of lymphoblastoma. Körte added two cases of his own in 1921, making the assertion that tumors of this type show characteristics of neither a true malignant tumor nor a specific process. He therefore suggested that they be classed as tumors of a nonspecific chronic inflammatory process. Liu, working in this clinic, added nine cases in 1925, frankly admitting his inability to distinguish malignant from nonmalignant forms. The term "chronic inflammatory tumor" has long been used in this hospital, but it is a poorly descriptive term, since it leads one to suspect neither the true tumor formation nor its origin and manner of growth. After consideration of all aspects of the question, Graves' term of lymphoblastoma has been accepted in this article as being the most descriptive, with certain modifications. Lymphoblastoma, according to Mallory's definition means "a tumor of mesenchymal origin of which the cells tend to differentiate into cells of the lymphocytic series." Further differentiation depends largely on the degree of malignant change exhibited by the tumor cells, and will be discussed more fully in a subsequent paragraph.

The small intestine seems peculiarly susceptible to this type of tumor. Twenty-one of the eighty-eight tumors of this series were diagnosed lymphoblastoma. They occur about twice as frequently in the small intestine as in the large. Comer and Fairbanks stated that 63 per cent of gastro-intestinal lymphoid tumors occur in the small bowel. Staemmler, classing such tumors as lymphosarcomas, placed the incidence at 62 per cent. It is sufficient to say that lymphoblastomas of the small intestine are by no means a rare occurrence, as is shown by Graves' collection of 249 cases from the literature.

This tumor may attack persons of any age, although statistics show that it occurs in young persons with far greater frequency than do other malignant tumors. The average age of patients included in this series was 32, the youngest being 5 and the oldest, 77 years. Distributed according to decades of life, this group was approximately equally divided between the first five.

White males show an apparent susceptibility to this tumor. Sixteen were affected as compared with five females, and eighteen of the patients were white as compared with three colored. This variation is greater than one can ascribe to chance, although it is impossible to account for it.

Lymphoblastomas show a striking predilection for the terminal ileum. All of the twenty-one cases here reported, with the exception

of one, were located in the terminal 100 cm. of the ileum, this one exception occurring in the middle third of the duodenum opposite the papilla of Vater. Several other instances were found in which the tumor involved the terminal ileum and the cecum together, but since it was impossible to determine the point of origin, they have not been included in this series.

Tumors of the lymphoid series do not metastasize as readily as either true sarcomas or carcinomas. The absence of this feature undoubtedly jeopardizes the estimation of their state of malignancy, and this has given rise to the chief difficulty in diagnosis. When metastases do occur, the adjacent mesenteric lymph nodes bear the brunt of the attack, but extension beyond them does not follow any set course. One patient showed a recurrence of the original tumor in the abdominal wall following operation. Another was operated on for a tumor of the brain, which was found at autopsy to be secondary to

TABLE 4.—*Distribution of Lymphoblastomas According to Age*

Age	Number of Tumors
1 to 10 years.....	3
11 to 20 years.....	4
21 to 30 years.....	2
31 to 40 years.....	4
41 to 50 years.....	4
51 to 60 years.....	2
61 to 70 years.....	1
71 years and over.....	1
Total.....	21

lymphoblastomas in the ileum. Kundrat attempted to explain metastasis from these tumors solely by way of the lymph channels. Ewing argued that in some instances secondary growths are found in locations that can be explained only on the basis of transportation by means of the blood stream. Such a view is supported by the second case just mentioned. In the face of such evidence it seems that one must assume that the malignant cells may be dispersed by either channel or by direct extension.

The gross pathology of lymphoblastomas is variable. Their size may vary from a small thickening of the wall in the region of the agminate nodules to that of a grapefruit, if the tumor is external in type. The most common form assumed by the tumor is that of a constricting growth encircling the lumen. This happens so frequently that it is almost characteristic of the tumor and supports the diagnosis of malignancy in cases of doubt. The growth begins on one side of the wall and extends around the lumen. Extension may also proceed in the longitudinal direction of the intestine followed by a dilatation in the center of the tumor, so that the final picture is that of a hollow sphere constricting the lumen at its points of entry and exit. Extension to the



mesentery may also take place, but this is not the rule. The majority of the tumors present smooth unbroken surfaces. Still another form sometimes found is that of multiple polyposis; these tumors resemble adenomas in their gross form, but they are microscopically lymphoid tumors. Such a condition might be designated as multiple lymphoblastomatosis.

The texture of the tumor, especially in the advancing edge is firm and fibrous, and the cut edge is bluish white. Central necrosis with excavation is not an unusual feature. Some of the latter type have been diagnosed abscesses when on incision of the wall a quantity of



Fig. 17 (path. no. 41291, case 3).—Gross specimen of a lymphoblastoma removed from the ileum at operation. The tumor resembles roughly a hollow sphere. The lumen was constricted at the points of entry and exit, while between the two there was a dilatation. The walls were thickened by invasion of the tumor. The mucosa was intact but hyperemic. The patient died three months later from recurrence (case of Dr. J. M. T. Finney).

purulent necrotic material escaped, and the malignant nature of the tumor was recognized only by frozen section.

The histologic picture is subject to the widest variation, although certain typical cellular elements are common to all types. Differentiation is based in general on the preponderance of these cells and is a modification of Ewing's classification. Thus there are four main groups: (*a*) nonspecific granulomas, (*b*) reticulum cell sarcoma, (*c*) malignant lymphocytomas and (*d*) endotheliomas.

*Nonspecific Granulomas.*—These tumors are most frequently found as inflammatory thickenings, polypoid growths or fungating masses in the lower ileum, but are rarely found in the constricting form. The overlying mucosa is seldom ulcerated, and the condition may pass unrecognized unless some form of obstruction occurs. With low power magnification the tissue is seen to consist of a cellular infiltration beginning in the loose connective tissue of the submucosa, and later invading the muscular coats, splitting apart the fibers but not destroying the normal architecture of the wall. The predominating cell is a small round cell which, with high power, resembles closely the lymphocyte of the blood stream. A small, light rim of cytoplasm surrounds the nucleus, which is also small and very dark-staining. Especially abundant are

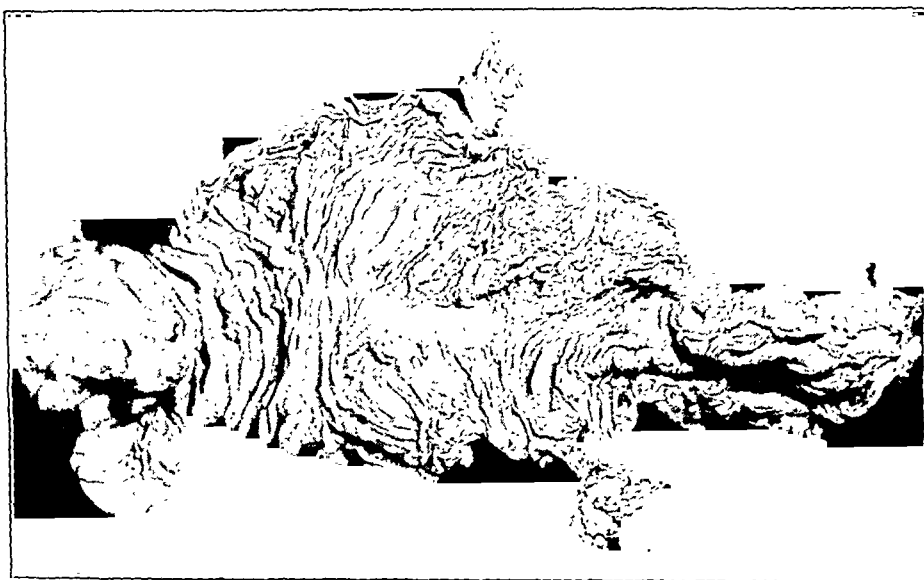


Fig. 18 (path. no. 18427).—Gross specimen of a large pedunculated tumor arising in the lower ileum and causing an ileocecal intussusception. The cecum and terminal ileum were resected, and the patient made an uneventful recovery. The histologic diagnosis was lymphoblastoma (case of Dr. J. M. T. Finney).

plasma cells with a slightly larger nucleus and a larger amount of cytoplasm. Polymorphonuclear leukocytes appear in fewer numbers, and in some sections eosinophils are found. The stroma consists of normal strands of connective tissue and muscle fibers, somewhat distorted but not grossly invaded or destroyed.

The symptoms of tumor as a whole are similar in many respects to those of a specific infection, and diagnosis is often extremely difficult. The absence of positive clinical data characteristic of a specific infection, however, point toward the diagnosis of a tumor of lymphoid origin.

*Reticulum Cell Sarcoma.*—One of this group of tumors apparently takes its origin from the reticulum cells of the primordial follicles and

cords, the so-called reticulum cell sarcoma (figs. 19 and 21). The microscopic picture is characterized by a preponderance of reticulum cells scattered irregularly throughout the tumor. These are large cells



Fig. 19 (path. no. G6346).—High power photomicrograph of a lymphoblastoma of the ileum. The cells are polygonal and irregular in size, and there is an abundance of reticulum. Occasional large giant cells may be seen, and throughout the tumor is an admixture of small round cells. This is the reticulum cell type of sarcoma.

with a light-staining nucleus, which shows numerous mitotic figures. The cytoplasm is abundant, irregular and takes a bright pink stain with

eosin. The reticulum is variable in amount, being almost negligible in some areas, while in others it constitutes a profuse fibrous overgrowth. There is a scattering of small lymphocytes, leukocytes, eosinophils, plasma cells and occasional large giant cells. The latter possess a nucleus with a diameter at least twice that of the reticulum cells and a narrow rim of cytoplasm. They stain more darkly than the average lymphoid cells. Their nature is obscure, but it is assumed that they represent atypical cells of the lymphoid series. Vascularity is not marked but it is not unusual to find capillaries that have been invaded by tumor cells. Fragments of mucosa and normal tissue of the intestinal wall are found, especially near the edges of the tumor, but little of the normal structure is left. The tumor is clearly invasive rather than infiltrative.

*Malignant Lymphocytoma* (fig. 20).—This is the type most commonly found and is the form usually confused with lymphosarcoma. It represents a misdirected development of the normal lymphocyte. It appears apparently first in the agminated nodules, where it rapidly increases in size, compressing and forcing out the normal structures of the lymph node, after which it grows by extension, usually in the constricting form described elsewhere. The predominating cell type is one that resembles closely a large lymphocyte. The nucleus is much larger, however, and vesicular with many or few chromatin particles. The cytoplasm is scanty and takes a light stain. It is very difficult to distinguish this type of cell from a reticulum cell when the reticulum is lacking. Some of the cells are smaller, but are clearly cells of the same series. They represent intermediate forms between the lymphoblast and the mature tumor cells. These cells are closely packed together with little or no supporting stroma. They have the appearance of a younger cell near the advancing border of the tumor, with the smaller, darker staining nucleus of the intermediate form. The same admixture of leukocytes and plasma cells with occasional giant cells is common to this as well as to the preceding type. These are especially marked near the borders of the tumor. Vascularity is marked, and capillaries are scattered throughout. These are peculiarly susceptible to the invasion of the tumor cells, and in places the endothelial lining is broken through and the lumen filled with malignant looking cells. The large giant cells already described are not an essential part of the picture, but large multinuclear cells are not uncommon.

*Endotheliomas*.—One must consider the possibility of endotheliomas arising from the endothelial cells of the lymph nodes. These, if they occur at all, are so rare in the intestine that a discussion of their pathology is unwarranted.

The histogenesis of the lymphoblastomas as a group is still obscure, but in an attempt to clarify the situation, it is assumed that these tumors

arise from lymphoid tissue as atypical cell types, for two reasons: First, practically all of them are found in the terminal ileum, where the agminate nodes are known to occur with the greatest frequency. Furthermore, it is not uncommon to find a tumor developing directly

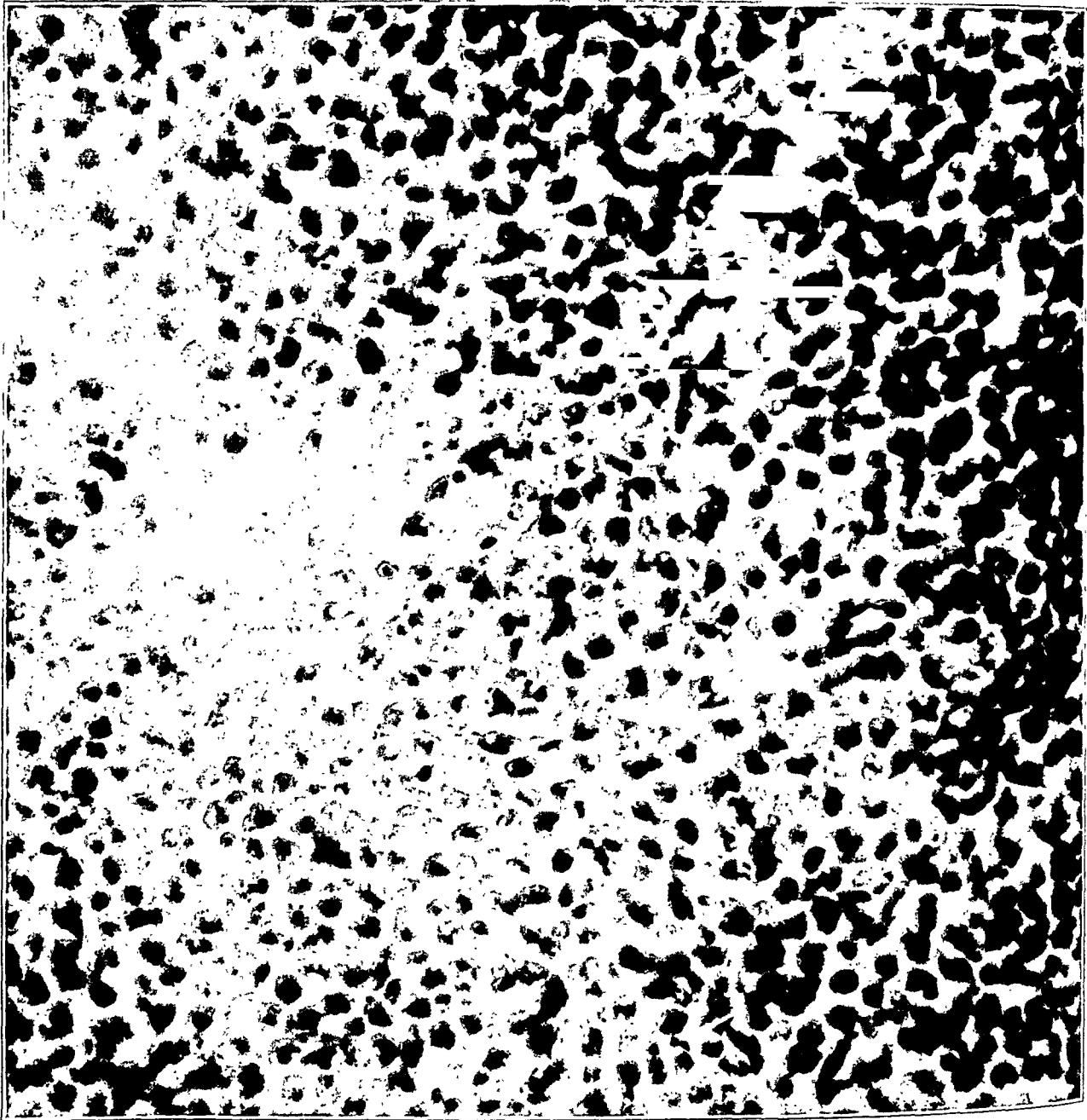


Fig. 20 (path. no. 16485, case 9).—High power photomicrograph of a lymphoblastoma of the malignant lymphocytoma type. The cells are densely packed together in a homogeneous mass. They are round but irregular in size. The cytoplasm is scanty, and the nuclei are large and hyperchromatic. Smaller cells resembling true lymphocytes are seen, and between the two types may be seen all stages of gradation. There is little or no reticulum or stroma (case of Dr. G. J. Winthrop).

from one of these nodes or patches as a proliferation of large atypical cells which disrupt the normal histology of the node and later penetrate the structures of the intestinal wall. In the second place, the cells comprising the tumor show plainly all gradations from that of a normal lymphocyte to the large, malignant tumor cell. What causes the lymphoblast to assume the malignant form is a different matter. Stasis

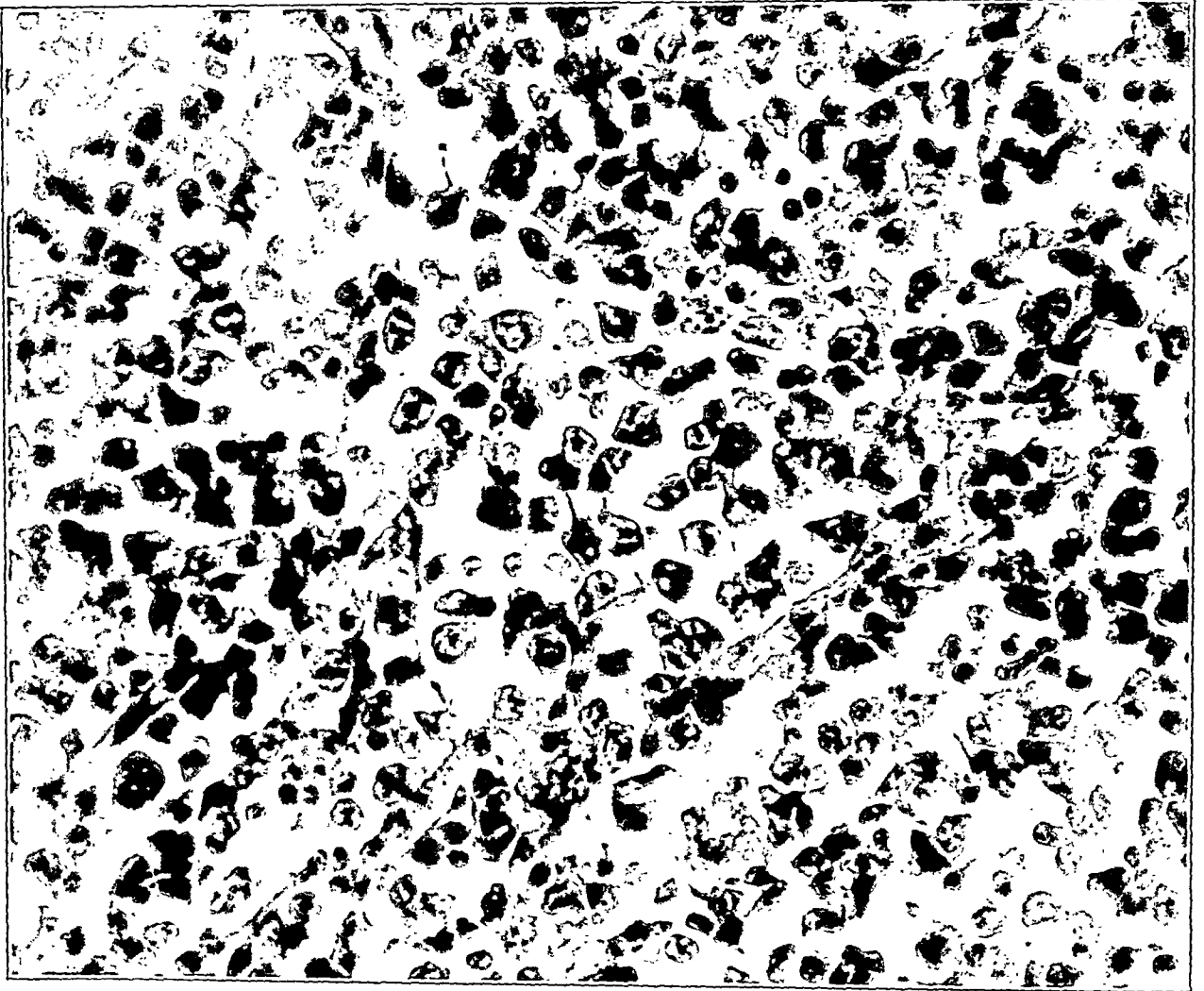


Fig. 21 (path. no. 41291, case 3).—High power photomicrograph of a lymphoblastoma. This is a reticulum cell sarcoma of a slightly different type from that shown in figure 19. The cells are large and polygonal, vary greatly in size, and are not so closely packed as in the preceding photomicrograph. The nuclei are large and vesicular, and the cytoplasm is moderate in amount. There is a moderate amount of reticulum scattered throughout the section. The tumor cells are invading a capillary in the upper portion of the picture.

and irritation, as discussed in a previous paragraph, may play a part, but this remains to be proved.

Assuming that the growth is of lymphoid origin, there remains the question of diagnosis, which is far more important. It concerns itself with two phases, that of classification and that of malignancy. For reasons previously stated this group of tumors is considered under the general heading of lymphoblastomas. Ewing, discussing the histogenesis of lymphoid tumors in general, classified them according to their three possible cellular prototypes as follows: 1. Lymphocytes may give rise to the benign group of lymphomas or granulomas or to the malignant lymphocytomas commonly known as lymphosarcomas. 2. Reticulum cells are the source of the reticulum cell sarcoma or large cell sarcomas. This is the tumor commonly referred to in the literature as round cell sarcoma and is practically always malignant. 3. Endothelial cells, may give rise to endotheliomas, although this type of tumor is rarely found in the intestine. It is possible to subdivide these groups further, but for practical purposes this is sufficient.

The second and by far the most important aspect of diagnosis is the determination of the state of malignancy of the tumor. The pathologist is accustomed to consider metastasis as the criterion of malignancy. Recurrence following the excision of a tumor is also indicative of malignancy. When this occurs the diagnosis is simple, but at this stage is not of prime importance, since the chances of curing the patient are very poor. It is a case of valuable "positive" and valueless "negative" information, for when metastasis has not occurred and the patient is presumably cured following excision, it is impossible to foretell the course of events had the patient been untreated. This cannot be relied on, therefore, for accurate diagnosis, and the best index of malignancy is the appearance of the cells themselves. Experience has shown that the reticulum cell sarcoma is the most malignant of this group. Nevertheless, since metastases do occur in instances in which the microscopic picture cannot be differentiated from that of tumors that remain localized, the lymphoblastomas must be considered potentially malignant until the clinical course has proved them otherwise.

The relation between certain infectious processes and the lymphoid tumors is interesting but confusing. That tuberculosis and syphilis sometimes simulate true tumors is well known. The cellular infiltration that they occasion is largely lymphocytic and the differentiation is very difficult in the absence of relevant clinical points. For obvious reasons specific infections have been omitted in this study since they form a discrete group in themselves.

Lymphoblastomas comprise a borderline group of tumors in regard to malignancy. Metastasis is not constant, and in cases in which it has not occurred the prognosis is good. Lymphoblastomas seldom recur following excision, but the surgical procedure should include

resection of a portion of the normal intestine on either side of the tumor. In any event, it is by far safest to consider the tumor as potentially malignant and to treat it as such.

## BENIGN TUMORS

### ADENOMAS

Adenoma is the type of benign tumor most commonly found in the small intestine. It seldom attains a size sufficient to cause obstructive symptoms, however, and the majority were recognized only at autopsy. Adenomas comprised fifteen of the eighty-eight tumors in this series, or 17 per cent. Herteaux placed this value at 14.3 per cent while King found it slightly higher, namely 19 per cent. Balfour and Henderson, considering only the benign tumors, found adenomas in 40 per cent of the cases. Saint, who has given the best review of the subject to date, put their incidence at 8 per cent of all tumors of the small intestine, but found them third in frequency among benign tumors.

The age limit is exceedingly variable. The youngest patient in this series was 6 months and the oldest 62 years of age, the average age being 33.5 years. Symptomatic adenomas tend to occur in younger people. No race and neither sex shows any particular susceptibility to this tumor.

Adenomas increase in frequency toward the lower part of the intestinal tract. In ten of the fifteen cases they were located in the ileum. King noticed this fact and commented on finding all of his five cases in the ileum. Golden reported eleven cases arising in the duodenum, however, five of which originated from the cells of Brunner's glands. All writers agree that adenomas of the jejunum are extremely rare.

The gross pathology of adenomas is similar to that of the majority of benign tumors. They comprise a large part of the group classed as polyps or papillomas, although the sessile form is not uncommon, especially in the early stages of the tumor. They usually occur singly, but may be multiple. Such a condition is known as multiple polyposis and may be widespread in the lower part of the ileum and colon. The tumors vary in size from the tiniest filiform thread, the diameter of a pinhead, to a mass as large as an English walnut. The latter are usually recognized only when they produce obstructive symptoms. Multiple polyposis is frequently indistinguishable from colitis by clinical symptoms alone. The gross appearance differs very little from that of other types of polyps. The mucous membrane is usually intact and has a deep reddish color as a result of hyperemia. It is often convoluted and follows the outlines of the tumor, dipping into the crevices and producing a fungating appearance. On section, the tumor is a mushroom-like mass, with a central white fibrous stalk leading up from



the intestinal wall and ramifying between soft, friable masses of glandular tissue lying at the periphery. The mucous membrane can be followed by the naked eye down to the point of union with the normal mucosa of the intestinal wall.

The glandular elements of a typical adenoma show two types of cellular development. There is less proliferation near the pedicle. The cells are very similar to those of normal intestinal epithelium, with dark oval nuclei lying at the bases of columnar cells which are distended with mucus. Approaching the periphery the cells became more carelessly arranged. The nuclei are often 3 or 4 deep, the cytoplasm is granular, and nuclear polarity is lost in a cell that is not of the pure columnar shape. The nuclei may be rich in chromatin and in some places resemble malignant cells.

The connective tissue stroma is composed of ramifications of the pedicle between the glandular elements of the tumor. It arises from the submucosa of the intestine and passes up into the tumor as a well formed band of connective tissue fibers and some muscle tissue. Well formed blood vessels are found in this pedicle. Toward the periphery, the stroma consists of fibroblasts and spindle cells and is much more cellular than the base of the pedicle. There is found in the former region an admixture of small round cells, large mononuclears, polymorphonuclears, eosinophils, plasma cells and red blood cells in large numbers. As the tumor grows older the differences in the cellular elements in the pedicle and at the periphery of the tumor become more marked. Saint attributes this to properties of the cell type. He classes those near the base as mucous cells primarily, while those at the periphery are undifferentiated cells the chief function of which is proliferation.

An adenoma may be defined as benign hypertrophy of the glandular epithelium of the mucous membrane. Two theories of etiology are recognized. Saint considers them inflammatory in origin and bases his conclusions on certain features characteristic of inflammation found coincident to the tumor, such as the presence of round cell infiltration, the occasional occurrence of *Oxyuris vermicularis* at the base of these tumors, their development in large numbers in the presence of inflammatory conditions, such as colitis, and their frequency in locations most subject to irritation. Hauser and Bordenauer attribute the development of the tumor to a primary epithelial change. Both theories are plausible, but in the light of the material studied in this laboratory, the first receives the better support.

The process of development of adenomas has been described by Saint as occurring in certain steps. These show the stages of growth so clearly that they are quoted verbatim. 1. There is a thickening in the mucosa, caused by hypertrophy and hyperplasia of the glandular

tissue which forms an upward fold. 2. There is a thickening of the submucosa, with an upward projection that acts as the forerunner of the pedicle. 3. The passage of feces and the peristaltic movements along the bowel exert pressure and traction on the fold, drawing it

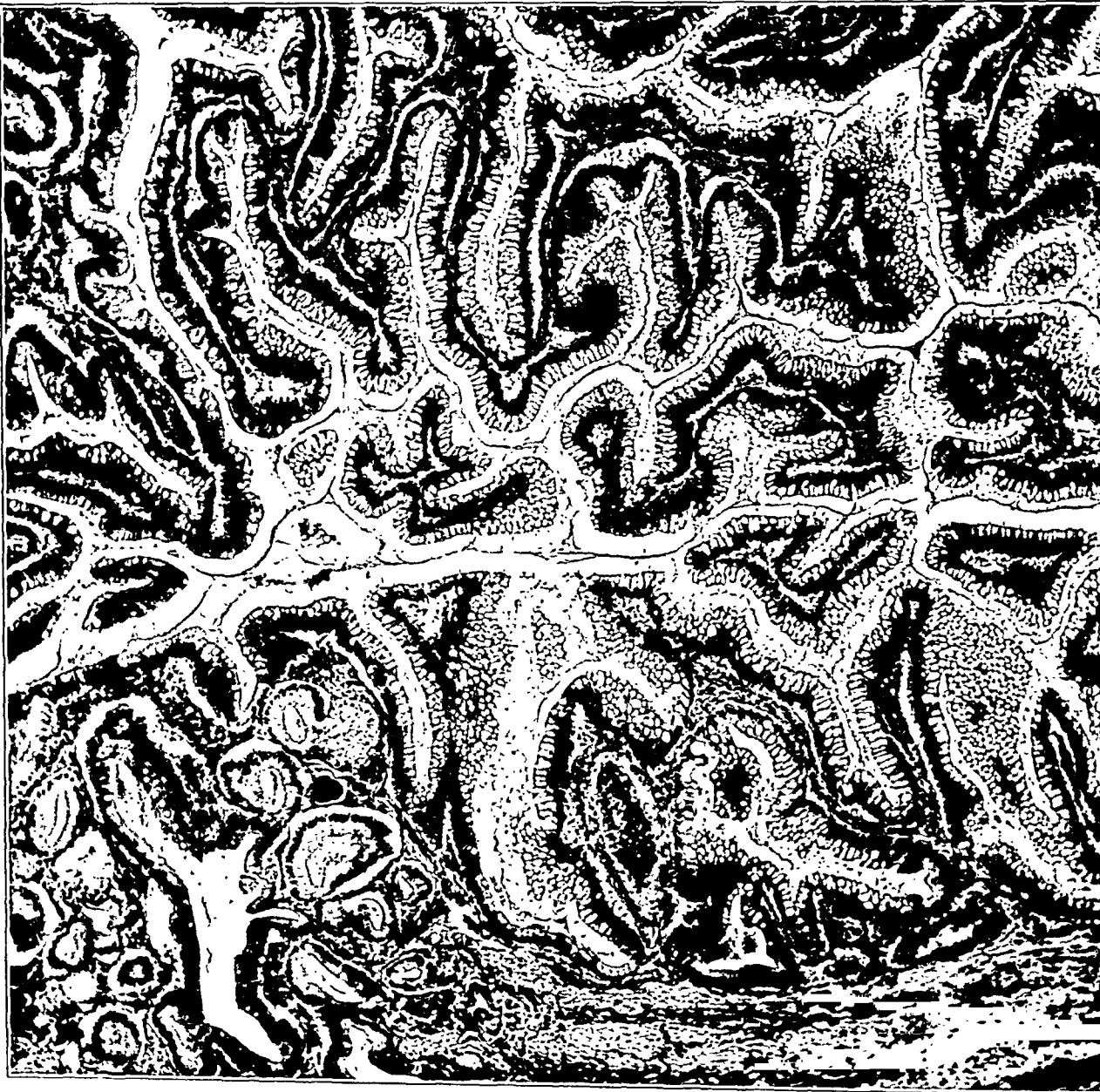


Fig. 22 (path. no. 38963, case 5).—Low power photomicrograph of a benign adenoma. Note the tortuous arrangement of the glands and the retention of the columnar cell type. Mucous goblet cells are especially numerous. There is little or no stroma.

out into the shape of the pedicle. 4. The proliferation of glandular epithelium from the center of the growth expands the head of the tumor into its mushroom form.

As a rule, the diagnosis of adenomas offers no difficulty, microscopically. These tumors are of relatively little importance clinically, except when malignant change has taken place, but for this reason must be regarded as a potential source of danger. This subject has been thoroughly discussed under the heading of adenocarcinoma.

#### MYOMAS

While myomas are not among the most common tumors in the small intestine, they do occur with sufficient frequency to warrant their consideration as a pathologic entity. Foerster first described this tumor in the small intestine in 1858. He found a small circumscribed nodule in the ileum opposite the mesenteric attachment which resembled closely in structure the myoma common to the uterus. Bottcher, in 1870, and Schatzler, in 1871, were the next to recognize the myoma as a definite tumor type in the intestine. Herteaux collected thirty-two cases in 1899, and in 1925 King brought the number up to forty-two. These authors found the frequency to be about equally divided between the small and the large intestines. The latter author considered the myoma to be among the three most frequent types of benign tumors, placing the incidence above that of adenomas. The figures of this series of cases, however, do not support this frequency, as only three cases were found.

Few conclusions can be drawn in regard to sex, race and age from so limited a number of cases. From data derived from collected cases, however, the decade in which these tumors are the most frequent is the fifth. Myomas have been found in persons as young as 13 and as old as 68 years. Males are more often affected than females in the ratio of 3:2.

The greatest incidence of myomas is in the ileum. Next in susceptibility is the jejunum, while the duodenum is rarely the seat of the growth. Staemmler found only 12 per cent of his cases in the duodenum.

The gross pathology of this type of tumor differs very little from that of other benign growths. Myomas may vary in size from that of a submucous nodule no larger than a pea to that of a large grapefruit or a child's head. They may grow either internally or externally, the latter type attaining the larger size. When internal, they are most commonly sessile, although the polypoid form is not rare. They are oval or round, circumscribed and feel freely movable beneath the mucous membrane, which is intact unless it has undergone pressure necrosis. They are thought to arise most frequently from the inner, circular layer of muscle, and opposite the pedicle attachment is sometimes seen a dimple-like depression in the serous surface. It is assumed

that the external tumors arise from the outer muscle layer and seldom distort the intestinal lumen, although there are exceptions to the rule. The latter may lie loosely in the peritoneal cavity, may grow retroperitoneally or in the layers of the mesentery. This form may be attached by either a broad base or a narrow pedicle.

The consistency of myomas, either internal or external is firm and rubbery. The color of the former is usually a deep red, owing to the extravasation of blood. Goldschmidt has commented on the hemorrhagic tendencies of myomas, terming them "bleeding myomas," and has emphasized the importance of melena in their diagnosis. On cut section, the tumor is bluish gray. The origin of the tumor from the muscle layer can often be traced by the naked eye.

The characteristic histologic picture of a myoma is that of benign hypertrophy of muscle fibers with an added overgrowth of fibrous connective tissue. The myomatous character is almost pure in young tumors and resembles very closely that of uterine myomas. The cellular elements consist of smooth muscle cells, rather larger than normal, but shorter and more rounded. The nucleus is larger and stains lighter than that of the normal cells. Numerous chromatin particles are present, but definite mitoses are absent. The periphery of the tumor is cellular, containing an infiltration of small round cells, plasma cells and mast cells, especially about the smaller blood vessels. The center of the tumor is frequently fibrous and grows faster than the periphery, and from this area alone can be confused with a fibroma. This feature has given rise to the mixed forms of fibromyoma and myofibroma commonly seen in the literature.

Myomas are subject to circulatory and regressive changes. Venous stasis produces capillary hemorrhages visible in the gross specimen as tiny red flecks. Occasionally, the hemorrhage becomes sufficiently large to cause pressure necrosis and cystic formation. Such a picture is regarded as a telangiectatic myoma. Hyaline degeneration is the most common regressive change, although calcification within the tumor has been reported.

So far as is known, the only possible points of origin of myomas in the intestine are the muscular layers, both internal and external, and the musculature of the arterioles. The latter source, while possible, is open to question. Certainly the most frequent source is the tunica muscularis. The three tumors of this series were definitely traced to this origin, and two of these could be seen to arise from the internal layer. Much can be said regarding the etiology, and little proved. Virchow was an exponent of the irritation theory, while Cohnheim considered the growth as a hypertrophy of misplaced germinal centers. Supporting the first theory is the somewhat general belief in irritation

as an etiologic factor in neoplastic growth. As Staemmler pointed out, however, if this were the causal factor, one would expect myomas to occur in places subject to the most irritation, and multiplicity would not be unusual. Present evidence favors the latter theory.

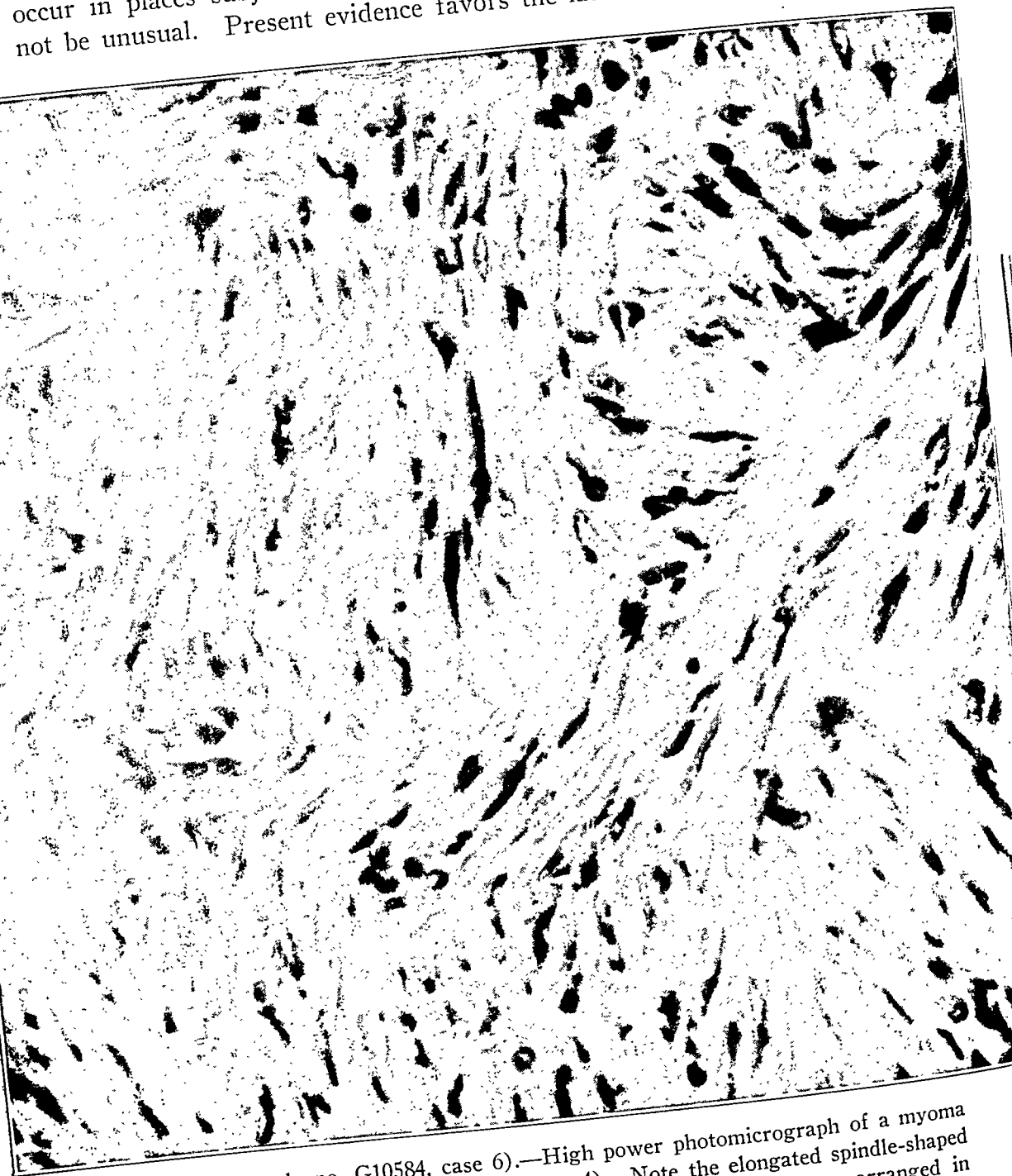


Fig. 23 (path. no. G10584, case 6).—High power photomicrograph of a myoma of the ileum (same tumor as that in figure 4). Note the elongated spindle-shaped cells containing abundant cytoplasm and oval nuclei. The cells are arranged in strands and whorls, and bear a striking resemblance to the sarcoma shown in figure 15.

The growth of this tumor is expansive in nature. It remains fairly well circumscribed, but may cause necrosis or atrophy of the sur-

rounding intestinal wall by pressure. Coincident with the expansion of the muscular element of the tumor, the fibrous stroma undergoes rapid hypertrophy, and it may be difficult to determine which tissue is predominant.

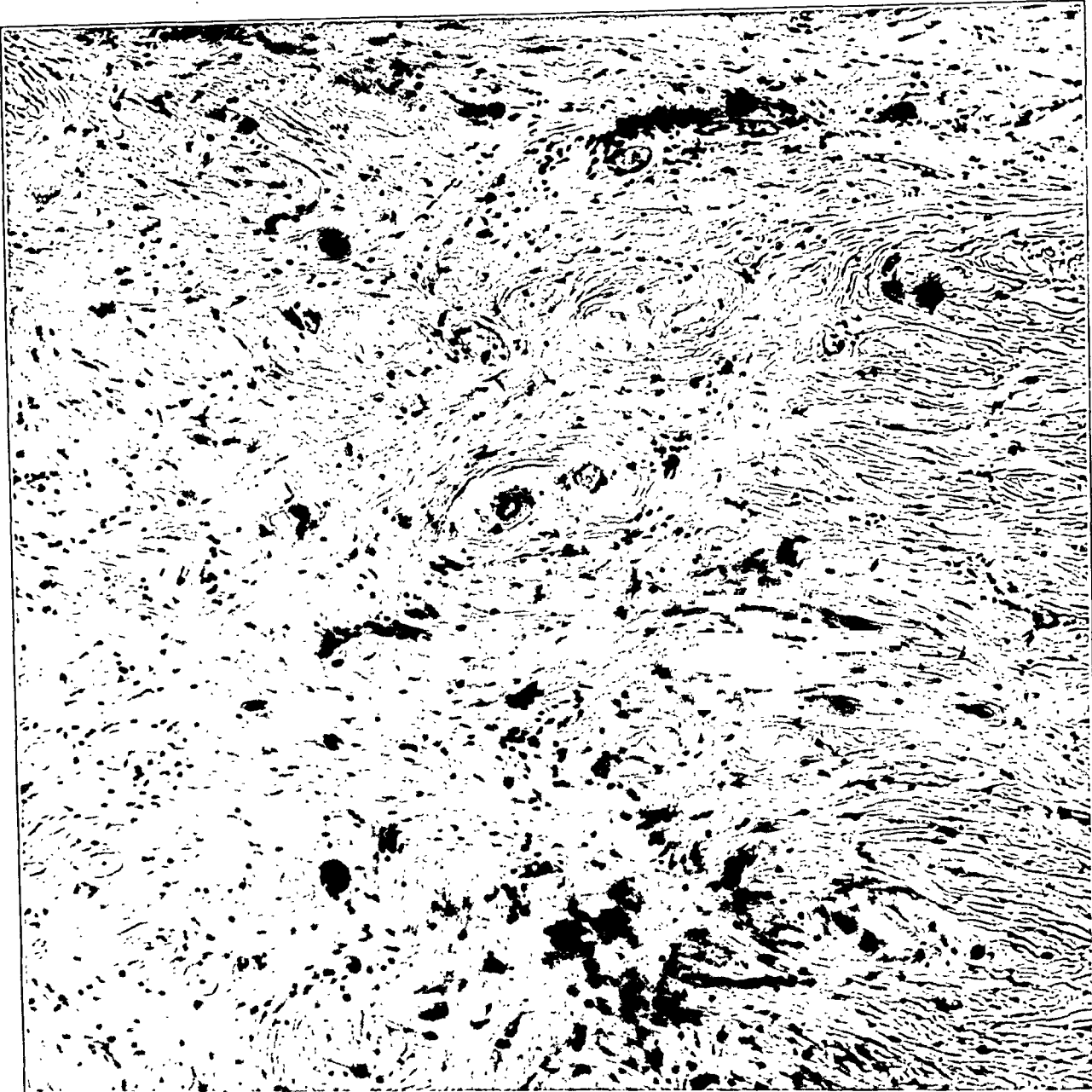


Fig. 24 (path. no. G3102).—Low power photomicrograph of a myoma of the ileum undergoing hyaline degeneration. The normal muscle cells are seen at the extreme right of the picture merging into the degenerating area. There is moderate cellular infiltration.

A word should be added in regard to sarcomatous change. The manner in which it occurs is not clear, but it is definitely known that

some myomas ultimately become malignant. The cells assume the characteristics of malignancy, and the tumor ceases to conform to the circumscribed limits of a benign growth.

#### FIBROMAS

Pure fibromas are among the rarest tumors found in the small bowel, but the mixed forms are much more common. Languet doubted the existence of the pure form at all. Nevertheless, thirty-nine cases, including the mixed forms, have been found in the literature that are considered authoritative. Four only were found in this series of cases. The frequency is no greater in the large intestine; in fact, most investigators of the subject consider that the fibroma holds a predilection for the small intestine.

This is a tumor primarily of advanced age. While some cases have been reported in children under 10 years of age, the majority occur in persons in the fifth and sixth decades of life. The youngest of the four patients was 52, the oldest 69 years of age. This is due in all probability to the fact that many tumors produce no symptoms and are found only at autopsy. There is no apparent racial distinction, the 4 cases being equally divided between the white and the black race. All four were in men, but this predominance is not borne out in the data from other reported cases.

The fibromas most commonly select the ileum as the site of growth, probably by reason of its greater extent. Cases are reported in the jejunum and duodenum roughly in proportion to their respective lengths.

There is nothing characteristic about the gross form of fibromas. They may grow internally as sessile or pedunculated tumors, or they may extend out into the mesentery, retroperitoneally, or they may be free in the peritoneal cavity as external tumors. Staemmler stated that the former predominate in the ratio 2:1. The mucous membrane is usually intact, but may be ulcerated and bleeding. The tumor mass is round or oval, discrete and circumscribed, and freely movable. It is firm and rubbery, and the cut section is grayish white. Some fibromas may assume a combination of the internal and the external forms and may appear as a large irregular mass which in the gross section looks malignant.

In the microscopic section, the bulk of the tumor is seen to consist of connective tissue hypertrophy and hyperplasia. It is relatively poor in cellular elements. Elastic fibrils are predominant and may be demonstrated by Weigert's stain for elastic tissue. Interspersed among these fibrils may be seen numerous spindle cells and stellate fibroblasts. The latter are more mature near the center of the tumor, with branching cytoplasm and small dark nuclei. In the younger sections at the

periphery, they contain less cytoplasm, and the nuclei are larger, stain lighter and are occasionally vesicular. There is a moderate admixture of small round cells, plasma cells and red blood cells at the periphery,

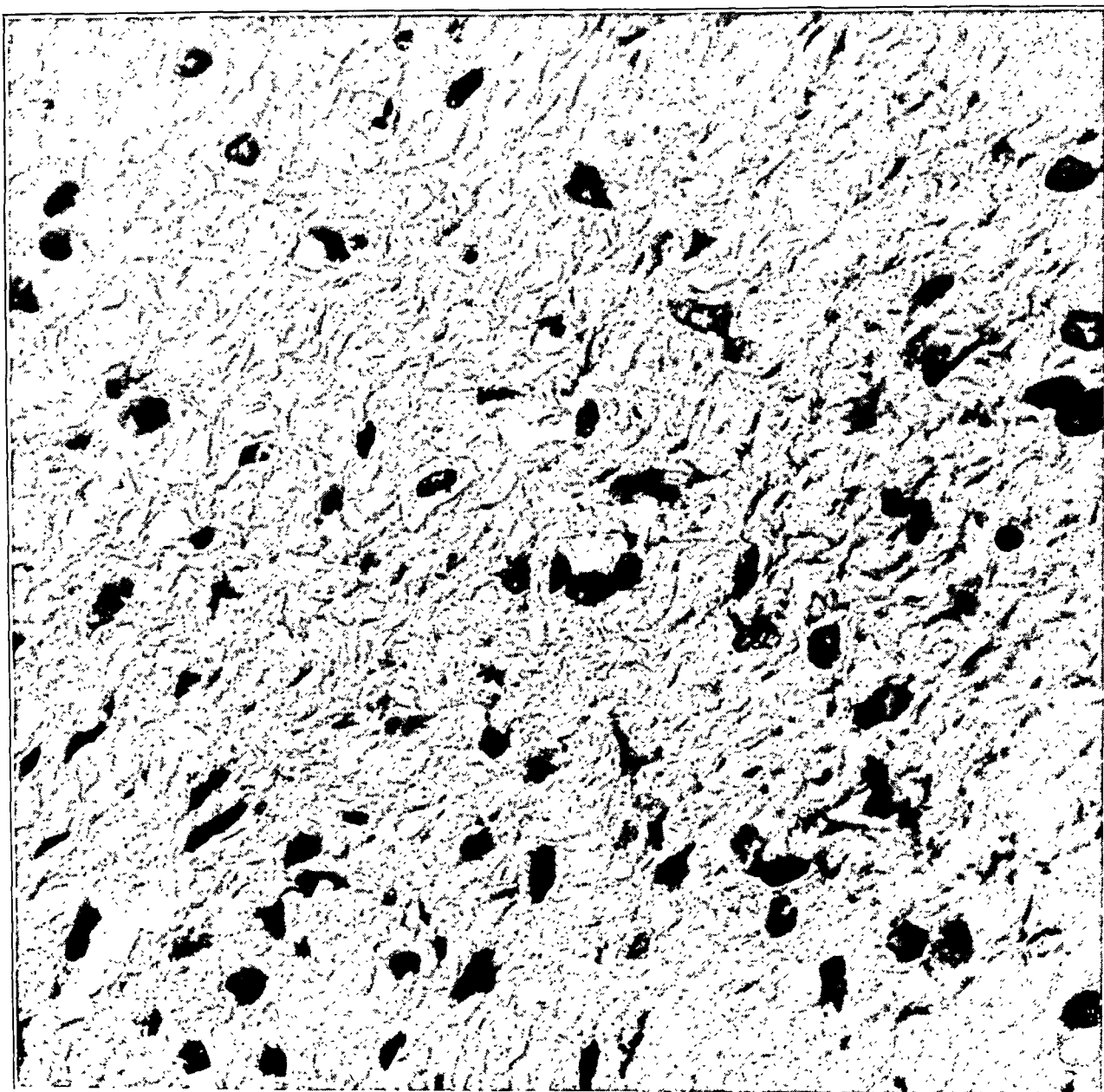


Fig. 25 (path. no. 46153, case 7).—High power photomicrograph of a fibroma of the duodenum. There is a dense overgrowth of elastic fibrous tissue among which are interspersed numerous large stellate cells with oval nuclei (case of Dr. Dean Lewis).

and in cases in which the mucous membrane is ulcerated and secondary infection has set in, leukocytic infiltration is marked.



Areas of myxomatous degeneration are not uncommon. Such an area resembles the pure myxoma in appearance, consisting of ramifying stellate cells enclosing a granular basophilic matrix. This tissue is grouped about small blood vessels, and vascularity is more marked in these areas than in other parts of the tumor.

Histogenetically, fibromas arise from connective tissue cells. The most frequent sources are the submucosa and subserosa, but periarterial connective tissue has also been considered as a possible point of origin. Herteaux considered the external form as arising chiefly from the subserosa, and the internal from the submucosa. The confusion between fibromas and myomas and the mixed forms is justified in that they often contain tissue of the two types, and it may be difficult to determine which is predominant and gave rise to the original tumor. The fibrous tissue seen in myomas is, however, of a secondary nature, and its chief function is that of a supporting stroma.

The origin of the myxomatous tissue is questionable. Some investigators regard it as an edematous form of the original fibroma. Others consider it as a specialized type of cell arising from the same tissue as the fibroma but retaining the property of secreting mucus. In either event, the presence of myxomatous tissue is of secondary importance.

#### ARGENTAFFIN OR CARCINOID TUMORS

The peculiar type of argentaffin or carcinoid tumor has aroused considerable discussion during recent years. Lubarsch, in 1888, first pointed out that this tumor, while resembling carcinoma histologically, was characterized by absence of metastases, lack of glandular structure and variation of the cell type from that of the normal mucosal cell. Nevertheless, he termed it primary carcinoma of the intestine. Numerous other cases were reported between that time and 1904, and the term carcinoid came to be used rather loosely to denote the resemblance to carcinoma in the absence of malignant characteristics. Trappe had stated that the origin of carcinoids could be traced to aberrant pancreatic rests which are not uncommonly found in the gastro-intestinal tract. The cells did indeed bear some resemblance to the cells of the islands of Langerhans, and the theory at that time found popular support. Bunting reported several cases in 1904 and commented on the similarity to the basal cell tumors of the skin described by Krompecher. Burkhardt agreed with this view, demonstrating the dissimilarity between carcinoids and pancreatic tissue and their likeness in clinical and pathologic respects to the basal cell tumors. Hubschmann, in 1910, suggested, in view of their yellow color, a possible origin in the chromaffin cells at the bases of the crypts of Lieberkuhn. Four years later, Gosset and Masson applied the silver impregnation method of staining to the

chromaffin cells and later to the carcinoid tumors, finding the presence of silver-staining granules. They, therefore, introduced the term "argentaffin" to apply to the carcinoids that took the silver stain. They also succeeded in demonstrating the similarity by microchemical means between these cells and cells of the suprarenal cortex.

This new conception of the carcinoids was accepted as plausible, but by no means universally. The work of these two authors was repeated by Hasegawa and Danish. Forbus reviewed all the available cases in this clinic in 1925. His article published at that date is the most complete recent work and contains an excellent historical review of the subject.

The clinical features of the carcinoids are insignificant. They rarely attain a size sufficient to cause symptoms and are rarely recognized before autopsy after death from other causes. Hence the age incidence is not characteristic. Likewise, the tumors show no predilection for either race or sex.

The majority of argentaffin tumors are located in the ileum. Five of the seven cases in this series were located in the ileum, one in the jejunum and one in the duodenum. This characteristic feature is further borne out by the great frequency of these tumors in the appendix, but one is at a loss to explain why they should select this particular region of the gastro-intestinal tract. The chromaffin cells, or cells of Kulchitzky, are, according to Maximow, scattered equally throughout the intestinal tract, and therefore offer no explanation of the fact.

The carcinoids are commonly thought to be benign tumors. During the past few years, however, several cases have been reported in which metastases had occurred and in which the malignant nature was diagnosed on this basis. One of the cases in this series was microscopically benign, but metastases had occurred to the liver and lymph nodes. The tumor was identified as a member of the argentaffin group by the silver stain. Cooke summarized 104 carcinoids from the literature and added eleven cases of his own. He found metastases in 21 per cent and concluded that malignancy is not uncommon. The author neglected to state if all of these tumors were proved to be true argentaffin tumors by the silver method of staining, however, and it is questionable if some of the so-called metastasizing carcinoids were confused with carcinoma of the medullary type, a resemblance easily appreciated by comparing figures 11 and 26.

The gross pathology of these tumors is not characteristic. They are relatively small, seldom more than a centimeter in diameter, more often the size of a pea. They may be sessile, within the intestinal wall or attached to a small pedicle. They are usually single, but may occur in groups of two or more. In one instance, two tumors were found attached

to the same stalk. The mucous membrane is usually intact, but it may be very thin and hyperemic in places. On cut section, the tumor is soft and elastic and yellow.

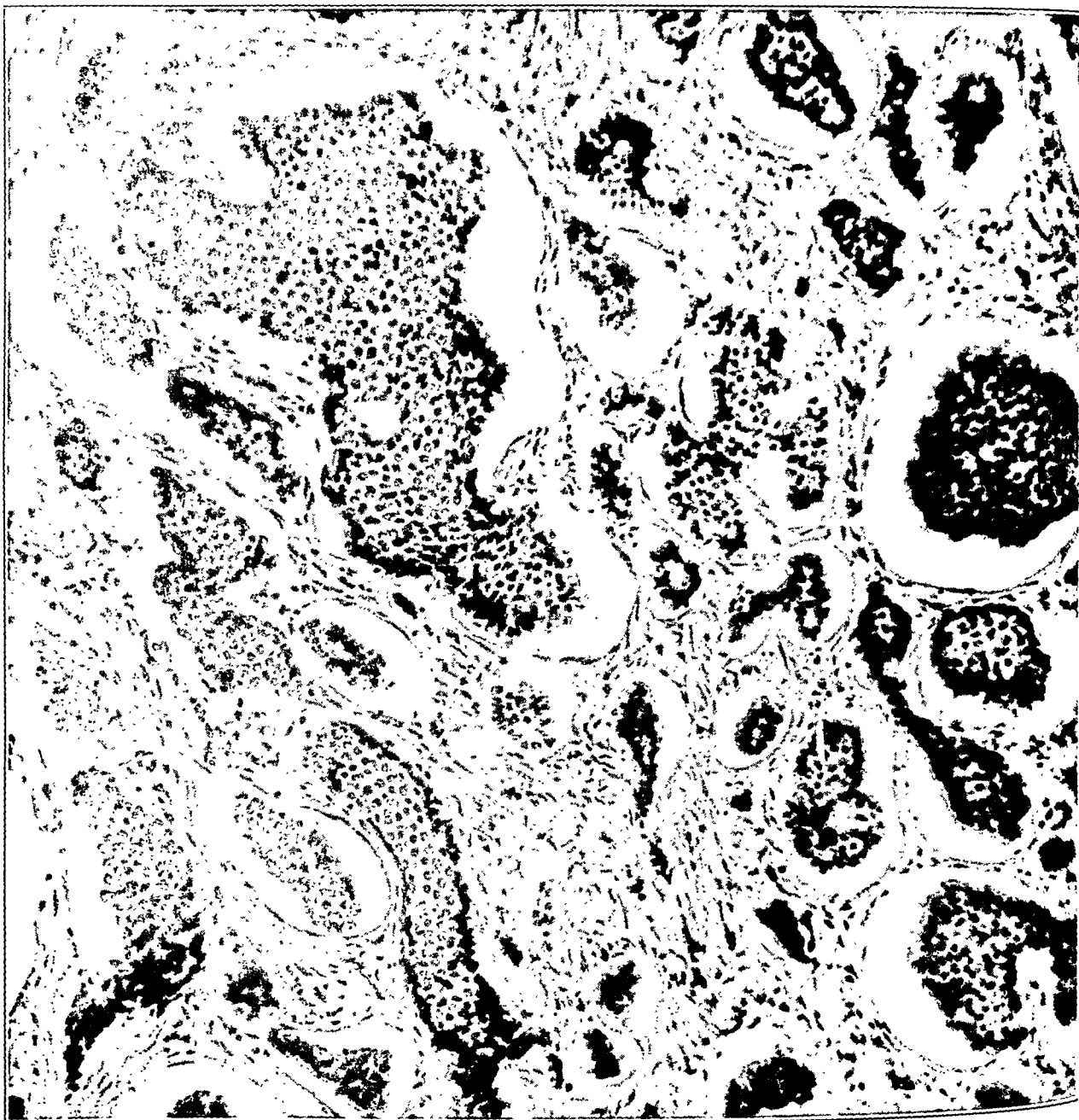


Fig. 26 (path. no. G6739, case 8).—Low power magnification of an argentaffin tumor of the ileum. The cells are small with indistinct outlines. The cytoplasm stains light with eosin, and the nuclei are small, round and dark. The cells are arranged in discrete nests with a dense connective tissue stroma. They were susceptible to the silver impregnation method of staining.

The characteristic microscopic picture is that of nests and strands of cells surrounded by a fairly definite limiting membrane and sepa-

rated by a stroma that varies in amount. The cells are small, relatively uniform, and round or oval. Near the edges of the nest of cells, pressure may cause them to assume a spindle shape. The cytoplasm

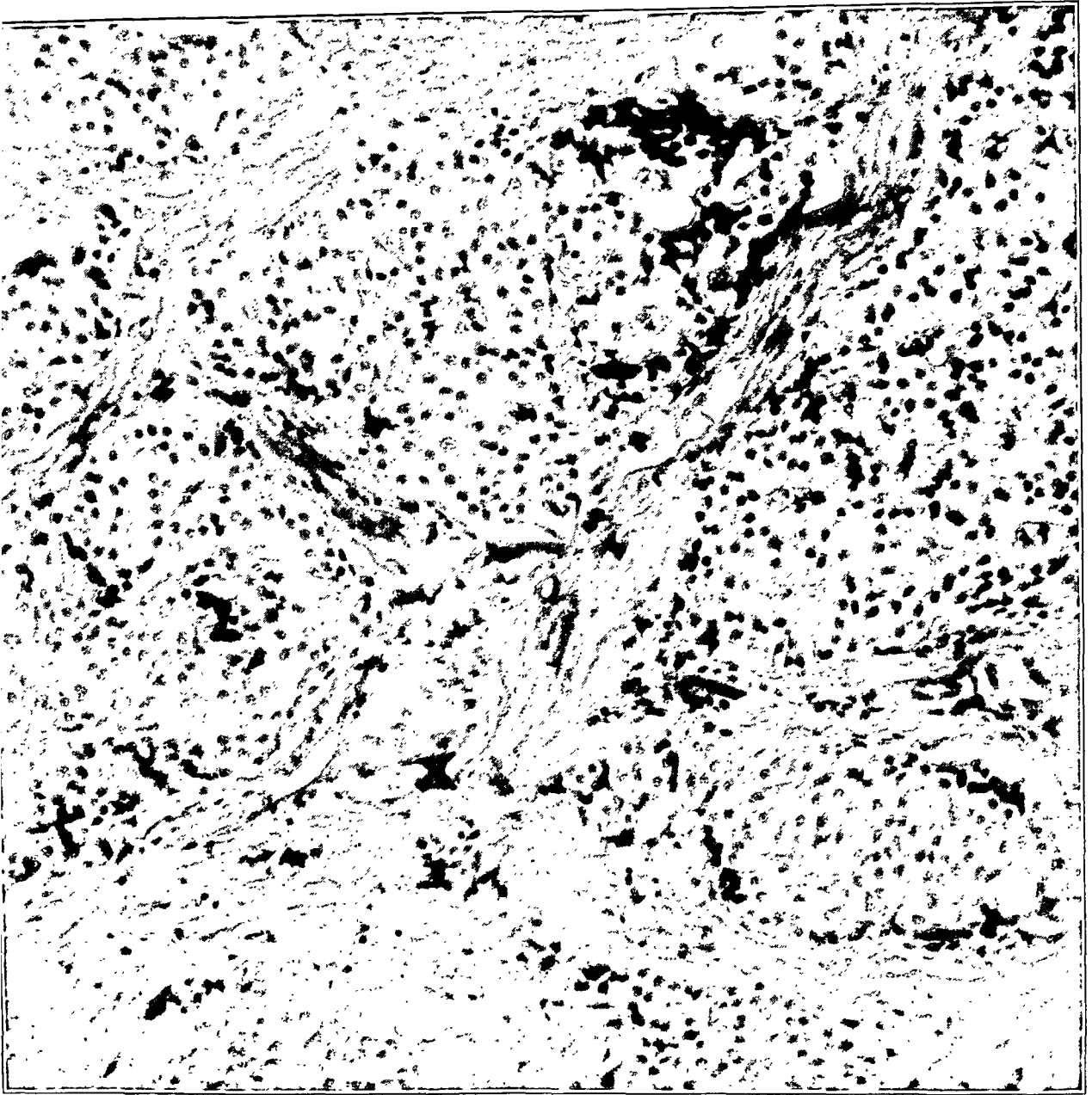


Fig. 27 (path. no. 36786).—High power photomicrograph of an argentaffin tumor of the duodenum. The cells are similar to those in figure 26, but the cytoplasm is more abundant, the cell outlines are more distinct, and a roughly alveolar formation is retained.

is pink-staining and varies in amount, in some tumors being abundant. The nuclei are rather large and conform roughly to the shape of the

cytoplasm. They take a light stain and are rich in chromatin. The stroma is formed of hyaline connective tissue in which are interspersed numerous small capillaries. Rarely, the cells assume an acinar formation, but the usual picture is that of solid sheets of cells.

Much remains to be explained regarding the histogenesis of argentaffin tumors. The theory of origin from pancreatic rests has had many adherents. Ewing classes these rests as a type of carcinoid. There are at least two features, however, that are not in keeping with this theory. The microscopic picture is definitely different in the two. The carcinoids do not show the acinar arrangement of cells characteristic of pancreatic tissue. The cells of the former, it is true, do resemble the cells of the islands of Langerhans known as the B type. Beyond that the resemblance ends. The second feature is the location. Pancreatic rests occur with greatest frequency in the duodenum, rarely in the jejunum and ileum. The carcinoids, on the other hand, are far more common in the lower part of the ileum and in the appendix, and are rare in the jejunum or duodenum.

The resemblance to basal cell epitheliomas of the skin, suggested by Bunting, is striking. So little is known regarding the origin and etiology of each, however, that it is impossible to consider them as analogous.

Forbus came to the conclusion, as a result of his study, that the endocrine theory of origin from the chromaffin or argentaffin cells was the most plausible, and in view of the present evidence, this is by far the most acceptable.

Very little can be added to the conception of these tumors from this study. The term carcinoid, although often used loosely, should not be discarded. It is a descriptive name and should be used to designate tumors that resemble the argentaffin tumors histologically. One cannot use the latter term accurately, however, until the diagnosis has been proved by the silver method of staining.

#### ABERRANT PANCREATIC RESTS

The aberrant pancreatic rest is a type of benign tumor growth that is of minor clinical significance. Nevertheless, it occurs with such frequency as to deserve brief consideration in any treatise on gastrointestinal tumors. The first cases reported in the literature were those of Klob in 1859. Warthin reported two cases in 1904, but neither occurred in the small intestine. The subject was reviewed in full in 1921 by Horgan. Simpson, working in this clinic in 1927, studied these tumors extensively, and his subsequent article is the most complete work of recent date. He collected a total of 157 cases from the literature, seventy-three of which were located in the small intestine.

These rests, like the preceding group of tumors, rarely produce clinical symptoms and are seldom found except at autopsy. Ages, therefore, mean little. The cases of this series were equally distributed between the sexes and races.

Assuming that pancreatic rests arise as misplaced embryonic tissue, it is logical to assume that the site of election is near the pancreas. This is borne out by the location of the tumors in this series. Two were found in the duodenum, three in the upper part of the jejunum and one near the midportion of the ileum. This distribution agrees closely with that noted by Simpson.

The tumors usually appear grossly as small submucous nodules, rarely more than a centimeter in diameter. They are irregular in shape, elongated, flattened or oval. Occasionally, they are of sufficient size to cause obstruction. One of the six cases here reported produced an intussusception of the ileum. The tissue is soft and spongy to touch, and is freely movable beneath the mucous membrane. The cut section is grayish white, and throughout the tumor can be seen irregular patches of denser tissue representing the pancreatic tissue.

The microscopic picture of pancreatic rests is essentially the same as that of normal pancreatic tissue, except for the distribution. When seen under low power magnification, the deep blue stain of the lobules stands out in marked contrast to the lighter pink interlobular connective tissue. The aberrant tissue may be scattered throughout the intestinal wall, but the largest accumulations are usually found in the submucosa. They may occur in compressed strands between the layers of the muscularis. Higher magnification shows the cells to be very similar to those of the normal pancreas. The cells are in acinar arrangement. The cytoplasm is abundant and basophilic, and zymogen granules are abundant. Normal islands of Langerhans are found in some sections, but are not constantly present, comprising one of the differences between the normal organ and the aberrant tissue. Excretory ducts lined by tall columnar or cuboidal cells are found in certain parts of the sections. Simpson has emphasized the resemblance of these ducts to adenocarcinoma in some instances.

Many theories have been elaborated to explain the development of accessory pancreatic tissue. That of Warthin is accepted at the present time in preference to the earlier theories of Zenker and Glinski. The former considered the growths as arising from lateral buds of the rudimentary pancreatic ducts as they pass through the intestinal wall in the embryo. They are thus segregated and carried either up or down as the intestine undergoes the process of longitudinal growth. Simpson observed the proximity of the ventral pancreatic bud in the embryo to the primitive yolk stalk, and believed that small buds might easily become detached at this point and be carried in either direction by the

later development of the latter structure. This theory is the most plausible offered as yet and goes far to explain the progressive infrequency of the growth toward the lower part of the intestine.



Fig. 28 (path. no. G10579).—Low power magnification of an aberrant pancreatic nodule found in the duodenum at autopsy. Note the acinar arrangement of the cells which are small and possess a granular, basophilic cytoplasm and small round nuclei. Occasional islands of Langerhans are found, and in the lower part of the photograph can be seen a dilated pancreatic duct.

The question of the relation of aberrant pancreatic tissue to diverticula of the intestine has been raised by several investigators. Koch

and Suzuki examined fifty cases of diverticulum and found pancreatic tissue at the tip of the structure in two instances. Albrecht and Arzi reported a case of Meckel's diverticulum to the end of which was attached an aberrant pancreatic nodule by a thin fibrous cord. The discovery of cases such as these has given rise to the theory that the accessory tissue existed first, and that the diverticulum was caused as a secondary result of traction on the tumor. The evidence at hand is insufficient to prove the theory, however, and it is doubtful if the occurrence is more than coincidental.

#### ANGIOMAS

True angiomas of the intestine are regarded by pathologists as being extremely rare in the small intestine. Herteaux was able to find only three cases. Helvestine reported a single case in 500 autopsies. Three cases are reported in this series. Two types are found, hemangioma arising from the vascular system and chylangioma arising from the lymphatic system. The latter tumors are classed variously as chylous extravasations and chylangiectases. They are commonly secondary to another pathologic process and possess little clinical significance unless large enough to cause partial obstruction of the intestinal lumen. Large hemangiomas sometimes become hemorrhagic and produce marked secondary anemia.

The clinical features of the angiomas are insignificant. No preference for age, race or sex has been demonstrated. One of the tumors was located in the duodenum, and two in the jejunum. There is no reason why the ileum should be excluded, and no doubt a larger number of cases would show an equal distribution throughout the small intestine.

Hemangiomas may be of two distinct types. The simple form consists of hypertrophy and overgrowth of the small blood vessels. The cavernous type shows in addition, large, dilated, blood-filled cavities and sinuses. Chylangiomas show the same types and in addition a more dilated form termed cystic, in which the supporting tissue tends to become atrophic. Multiplicity occurs in a large number of cases. Two of the three cases consisted of multiple nodules scattered along their respective channels of supply.

The gross appearance of the tumors differs slightly. Hemangiomas are small, reddish, submucous nodules, rarely more than a centimeter in diameter. The mucosa is seldom broken, but is hyperemic, and bleeding from the tumor is not uncommon. On section, the cut surface of the tumor is red, and blood may be squeezed from the interstices, leaving a porous spongelike mass. Chylangiomas, on the contrary, are grayish or yellow and softer, and on squeezing, a clear yellow or milky



fluid is expressed. Section reveals the tumor composed of cystic dilations of varying size separated by thin septums or spongy tissue according to the individual case. The smaller nodules may not be visible to the eye, but can be recognized by palpation. The larger tumors may cause a prominence on the serous as well as on the mucosal surface.

The characteristic microscopic picture of simple hemangiomas is an overgrowth of blood vessels. These are small and are arranged in tortuous masses or whorls. The capillary walls are composed of large endothelial cells, shorter and more plump than normal, with large light nuclei, and may be two or three layers deep. The vessels are separated by a connective tissue stroma which may or may not be densely infiltrated with cells of the myeloid and lymphoid series. The cavernous type consists of large blood-filled spaces which are lined with a single layer of endothelial cells. The cystlike structures may be filled with fibrin in old tumors. The septums are thin and composed of a scant connective tissue in which may be interspersed a few muscle fibers. The cavities are smaller near the edge of the tumor, and, in fact, one often recognizes both types of angioma in the same section. The simple form is predominant near the borders of the tumor, with dilatation increasingly greater near the center of the growth.

Chylangiomas are very similar in appearance. The new growth can sometimes be seen arising from and continuous with the lymphatic channels. The cystic spaces are larger, as a rule, and, instead of blood cells and fibrin, they contain a gelatinous pink-staining material through which are scattered a few leukocytes and epithelial cells.

The histogenesis of the angiomas remains somewhat confused. Jordan described three plexuses of blood vessels in the intestinal wall. These are the submucous, intermuscular and subserous. There are thus three possible sites of origin, although, judging from the customary location of the tumor in the submucosa, the first is by far the most common. Rokitansky considered the growth as a mere hypertrophy and overgrowth of vessels. Virchow contended that irritation and trauma were largely responsible for this phenomenon. Thoma, while accepting these factors to a limited extent, felt that hypertension combined with weakness of the vessel walls played an important part in the process.

Chylangiomas are thought to arise from the lymphatic plexus in the submucosa into which the lacteals of the villi empty. Two theories of etiology have been offered. Many writers believe that the tumor develops from misplaced embryonic tissue, but evidence to support this is lacking. That the cause is stasis and back pressure brought about by blockage of the mesenteric glands seems more plausible. The cystic appearance of the tumor is more suggestive of a dilatory process than a hypertrophy. Such cases are so rare that a comprehensive study of the subject is difficult.

Hematomas are not true tumor growths, and are mentioned with angiomas only in view of the fact that symptoms are sometimes produced resembling those of other tumors. They are extremely rare, and no mention of hematomas of the small intestine as a clinical or pathologic entity has been found in the literature. They are apparently purely mechanical in origin, consisting of an intramural extravasation

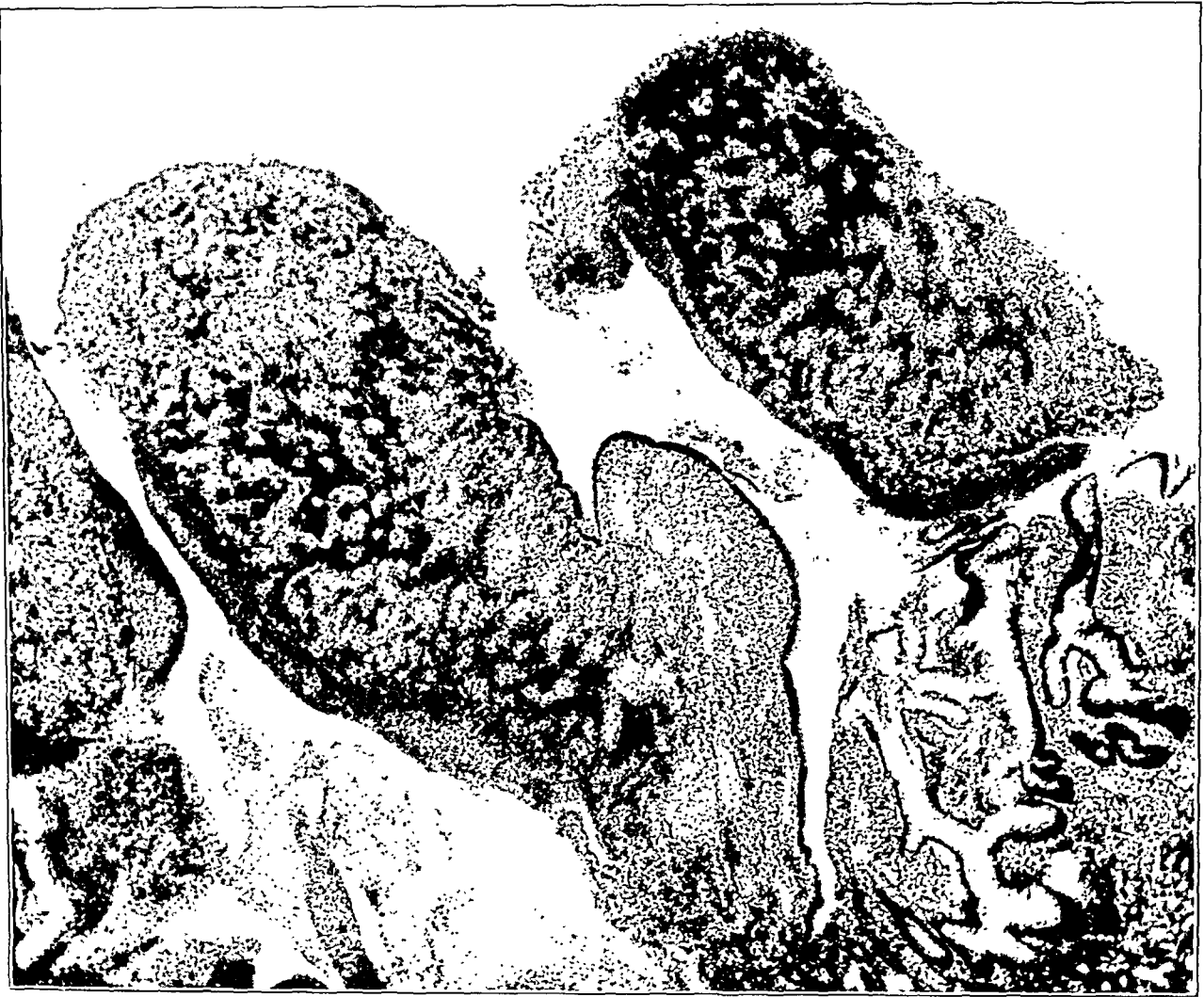


Fig. 29 (path. no. 24867, case 10).—Low power photomicrograph of a hemangioma of the ileum. The tumor has grown outward in fungating polyps composed largely of hypertrophied capillaries. They are covered in part by epithelial cells, and there is a dense infiltration of small round cells throughout. Note the normal mucosa in the lower right corner.

of blood, without any evidence of cellular hypertrophy. The etiology is not known. Hypertension, together with pathologic weakness of the vessel wall due to trauma, irritation or necrosis are factors to be considered. One case was found following postoperative mesenteric

thrombosis. It is conceivable that the stasis and back pressure caused by the blockage of the vessel brought about the rupture of the vessel.

These tumors have little clinical significance, unless the extravasation is sufficiently large to cause a partial occlusion of the intestinal lumen.

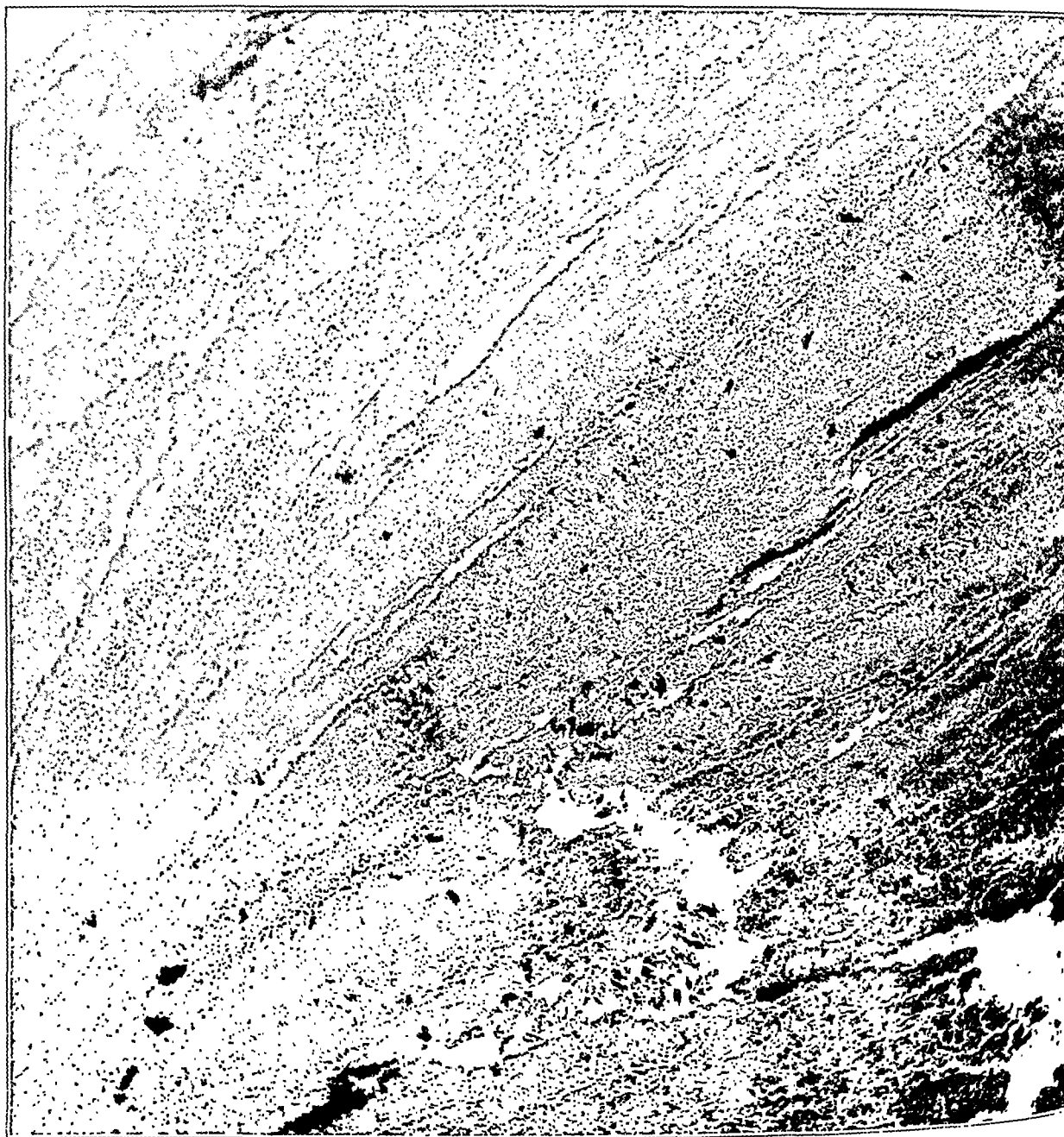


Fig. 30 (path. no. G9819, case 11).—Low power photomicrograph of a hematoma of the ileum causing partial obstruction. The organized blood clot has split apart the longitudinal fibers of the muscle coat and the submucosa in a fan-shaped manner. There is moderate leukocytic infiltration.

This was the condition brought about in one of the cases here reported. Both cases occurred in elderly white men, one aged 77 and the other

78 years. The condition may possibly be related to old age. Both tumors occurred in the ileum, but any part of the small intestine is susceptible.

The gross appearance of the tumor is that of a smooth oval or rounded semispheroid mass in the intestinal wall, lifting the mucosa and projecting into the lumen. Both cases were internal, although tumors of the external type can arise in the same manner, especially if the hemorrhage occurs in the subserous plexus. The mucosa may be intact at first, but later it may become gangrenous and necrotic from the effects of pressure. The tumor itself is hard and firm after the blood has clotted and organized. The cut section is dark red or black, resembling a fresh clot or an organizing thrombosis.

Very little can be seen in the microscopic section except a typical blood clot. Depending on its age, this may be fresh red cells with strands of fibrin or, if older, laminae of platelets with bordering accumulations of leukocytes with intervening strands of fibrin. The tumor is not encapsulated, but infiltrates and splits apart the normal tissues, in some places causing atrophy and necrosis. There may be a moderate round cell infiltration about the edges, if the condition has existed for any length of time.

#### LIPOMAS

Small, soft yellow nodules are not infrequently found in the small intestine at autopsy, which are found on histologic examination to be lipomas. They are by no means rare, but seldom cause symptoms before death results from other causes. Odelberg reported thirty-three cases, found in the literature, in his review of the subject and stated that 25 per cent. of all intestinal lipomas occur in the small intestine. Seven cases are reported in this series, comprising 8 per cent of the total.

This type of tumor is of minor clinical significance for two reasons. The rate of growth is very slow; from three to five years are necessary for it to attain a size sufficient to cause symptoms. In the second place, it seems a peculiarity of the tumor that it is attached by a long slender pedicle which frequently is broken, permitting the tumor to be passed per rectum. Nevertheless, lipomas on some occasions reach a large size, and, if internal, produce intussusception with its concurrent symptoms. If external, they may attain the size of a child's head, though such cases are extremely rare. None of the six cases here reported gave symptoms or were recognized before death. The occurrence of lipomas in elderly people indicates nothing more than the fact that death of the patient is usually brought about by causes other than the tumor. White men are apparently most susceptible, but there is no

explanation for this fact. There is nothing significant in the location of the tumors, as they are evenly distributed throughout the intestine.

Lipomas occur singly as a rule, but not infrequently from six to eight tumors are found in a single patient. Multiple lipomatosis is

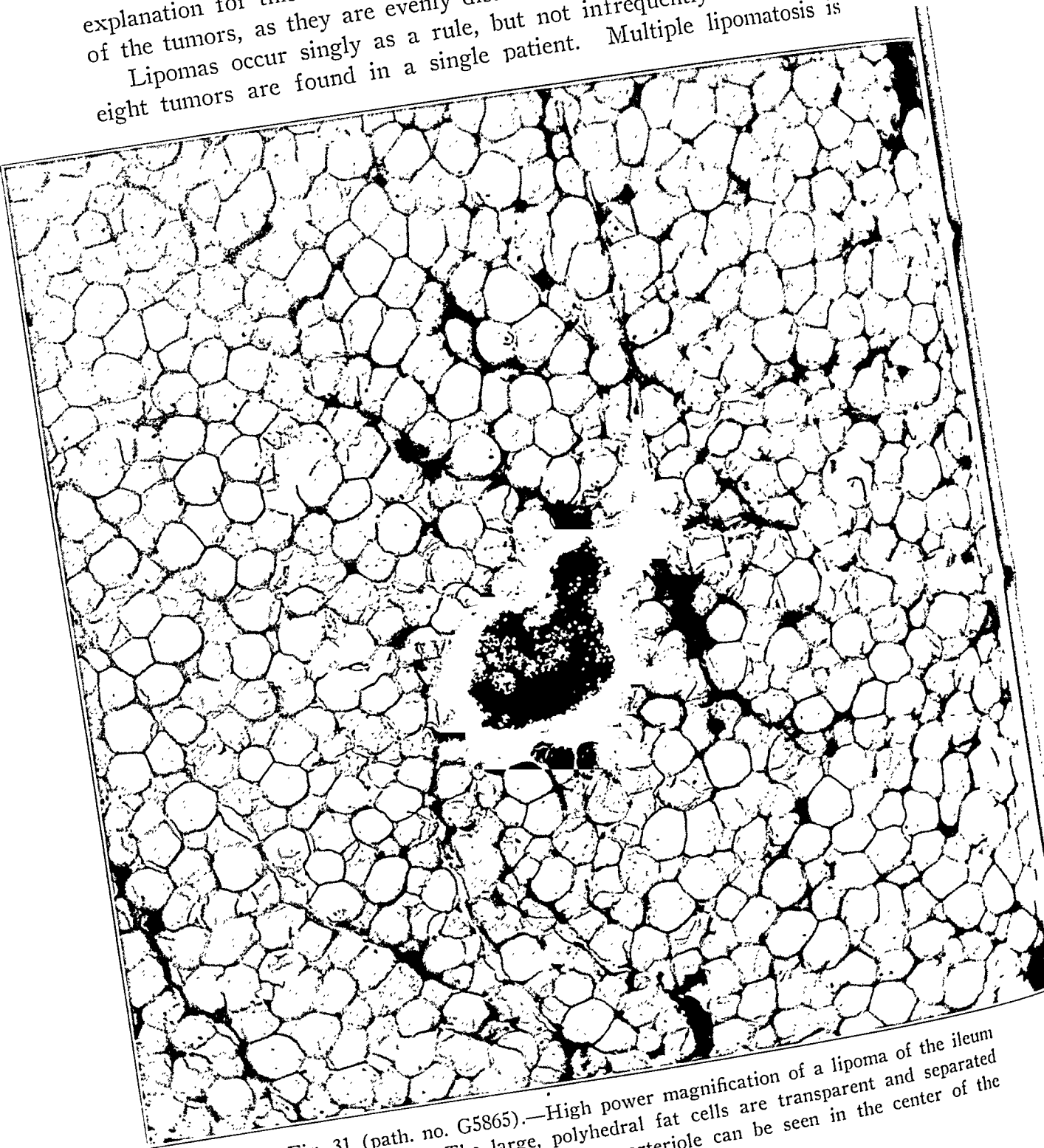


Fig. 31 (path. no. G5865).—High power magnification of a lipoma of the ileum found at autopsy. The large, polyhedral fat cells are transparent and separated by delicate fibrous septums. A large arteriole can be seen in the center of the picture.

rare. Eighty-five per cent of the tumors were internal in type. They rarely assume a size of more than from 1 to 2 cm. in diameter. They are

soft to touch and light yellow. They may be sessile in the younger stages, but tend to become pedunculated as they grow older, attached by a slender, delicate thread that is easily broken by the traction of the passing intestinal contents and peristaltic movements. The mucous membrane is intact unless ulceration has resulted from secondary infection. The cut section is yellow and resembles normal fatty tissue found elsewhere in the body.

Microscopically, intestinal lipomas are similar to those found elsewhere in the body. The cytoplasm of the fat cells is abundant and takes a very light stain. The nuclei are situated near the periphery and are small, oval and take a dark stain. The cells near the center of the tumor tend to be larger than those at the periphery. They are separated by thin septums of connective tissue, and occasional fibroblasts are found at the junction of 2 or more septums. Vascularity is not marked, but fine capillaries may be found in the interstices. The tumor is a composite growth, and, while it has no definite limiting membrane, it is sharply delineated from the surrounding tissues. It is not an invasive growth, evidently starting about a central nucleus and expanding concentrically. Round cell infiltration may or may not be present near the edges of the tumor. Hemorrhage resulting from necrosis has been observed as a secondary change, and, when present, is recognized by the presence of occult blood in the stools.

A smaller cell type of tumor has been described which resembles the xanthomatous type. It is termed lipoblastoma, but is difficult to demonstrate.

The origin of lipomas in the intestine is thought to be from areolar tissue in the submucosa or, in some instances, from the subserosa. The etiology is uncertain. Staemmler regarded them as arising from heteroplastic fatty tissues, while Erlich considered the growth as a simple hyperplasia of fat cells. Odelberg suggested the contributing factor of stagnated intestinal contents, but this is at best hypothetical. The large external lipomas arising from the subserous areolar tissue are thought by some to have a prototype in the appendices epiploica.

*(To be Concluded)*

# Fiftieth Anniversary of the Removal of the Gallbladder

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CARL LANGENBUCH—"MASTER SURGEON OF THE  
BILIARY SYSTEM"  
1846-1901

BÉLA HALPERT, M.D.  
NEW HAVEN, CONN.

Carl Langenbuch, der die Ektomie erfand und für die Ausführung der Choledochotomie, Choledochoduodenostomie und Cholangio-Enterostomie ganz genaue Anleitung gab, verdient den Namen "Meister." . . . Langenbuch hat in der Chirurgie der Gallenwege überhaupt alles ersonnen, was zu ersinnen war, und so ist es bisher diesem einen Meister geblieben.—*Hans Kehr, 1913.*

(Carl Langenbuch, who first devised ectomy and who gave detailed instruction for choledochotomy, choledochoduodenostomy and cholangioenterostomy, deserves the name "master." . . . In the surgery of the biliary passages Langenbuch has thought out everything that was to be thought out, and so far he has remained the only master.)

In the surgical clinics, all over the world, operations on the biliary system are of almost daily occurrence. Thus, it is strange to realize that the first cholecystectomy in man was performed hardly half a century ago. It was Carl Langenbuch, the chief of the Lazaruskrankenhaus in Berlin who, on July 15, 1882, removed surgically a diseased gallbladder with its calculous content and thus effected a miraculous cure of a patient long incapacitated by his painful ailment of chronic cholecystitis and cholelithiasis. The approaching fiftieth anniversary of this operation seems a fitting occasion for inquiring into the life of the man and an opportunity for paying tribute to the memory of the physician whose ingenuity and courage rendered the biliary system accessible to surgery. The writings of Carl Langenbuch and the necrologies written mostly by personal friends of his are a rich store of data about his personality and character. And thus, though distant from the available local sources of information and from his still living contemporaries, it is possible to gain a fair acquaintance with Langenbuch and to view him at the most outstanding periods of his career.

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From the Department of Surgery, Yale University School of Medicine.

Carl Johann August Langenbuch was born on Aug. 20, 1846, in Kiel. Here he attended the local Gymnasium, and in 1865 enrolled in the University of Kiel to study medicine. He graduated from this university in 1869, with a dissertation on ruptures of the aorta, obtaining the degree of doctor of medicine at the age of 23. Summoned for military service, he took an active part in the war between Germany and France. Being intensely patriotic, he retained a deep interest in warfare and in all medical problems connected with it. On his return from this war, he became Wilms' assistant for two years (1871-1873) in the Krankenhaus Bethanien of Berlin, acquiring there a surgical training. Langenbuch's opportunities came early and while he was still rather young. His reputation grew steadily from the date of his appointment as director of the newly organized Lazaruskrankenhaus (1873) until his untimely death on the night between June 8 and 9, 1901, at the age of 55.

As director of the Lazaruskrankenhaus in Berlin, Langenbuch was head of both the medical and the surgical divisions, a singularly advantageous position for creative work for a man of his ability and training. A glance at the list of his publications proves sufficiently that he made the best of this opportunity.

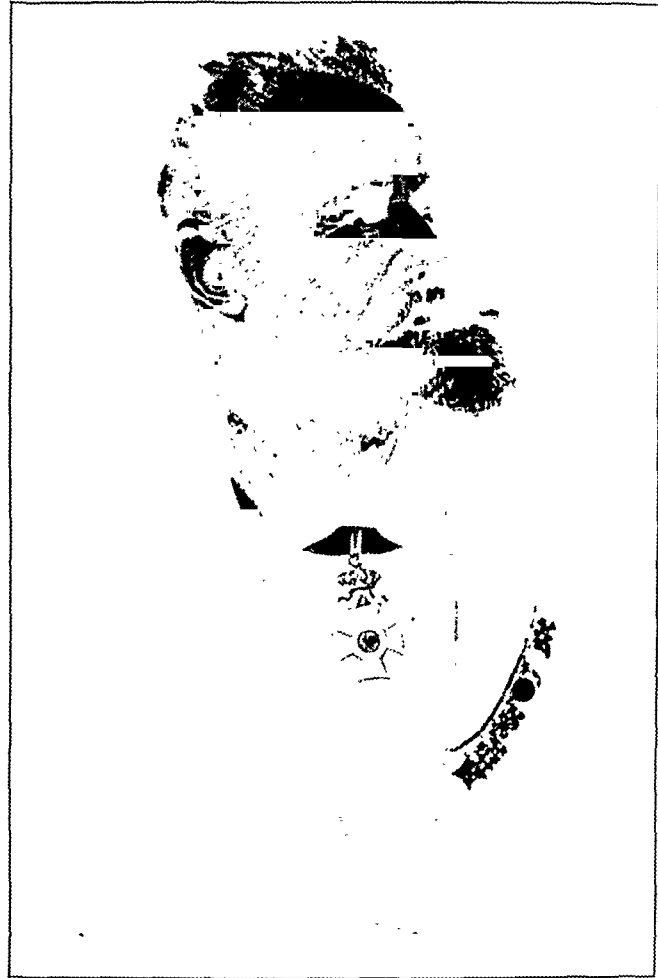
Among the members of the German Surgical Society, the name of Carl Langenbuch appeared for the first time on the list of those present at the Third Congress, held in 1874. Although he attended each subsequent year, it was not until the Eighth Congress that his name appeared on the program. In the first session of this congress, April 16, 1879, Langenbuch discussed Langenbeck's paper on pharyngotomy, suggesting that the epiglottis be utilized to close the entrance to the larynx in order to eliminate retching and the danger of aspiration pneumonia. In the subsequent session he demonstrated a huge urinary calculus which was removed from the bladder at necropsy of one of his patients, and also the organs of a 70 year old man with situs inversus.

At the Ninth Congress (1880) Langenbuch had a variety of specimens to show: a bony tumor that he had successfully removed from the orbit of a young woman; peculiar, large concretions, one of which was removed by enterotomy from the jejunum, and two more discovered at necropsy of a man who died shortly after operation; joint mice of traumatic origin, removed from the knee joint of a train clerk; the stomach of a 19 months old child on whom nine months previously a gastrostomy had been performed because of stricture of the esophagus; the specimen from a young woman who had a carcinoma of the stomach and on whom he performed a duodenostomy, the very first such operation ever performed.

At the Tenth Congress (1881) Langenbuch presented a brief history of two patients in each of whom, because of disabling symptoms of



wandering kidney, right nephrectomy was performed by the then customary transperitoneal approach with the modification of carrying the incision along the lateral margin of the rectus muscle instead of in the median line as was the practice at that time. He also gave the history of two other patients in whom lesions of the spinal cord were treated by nerve stretching. In the discussion Langenbuch remarked that he had



*Karl Langenbuch*

stretched the sciatic nerve in twenty-four cases with beneficial results. At other sessions of the same congress he discussed Zeller's paper, making mention of the fact that he performed a total extirpation of the larynx in an old woman some two years previously. He also showed two patients: one, with a chronic empyema, in whom he had removed

portions of the fifth to ninth ribs, from 5 to 12 cm. in length, and another in whom he had sutured a fractured patella.

At the Eleventh Congress (1882) Langenbuch discussed the papers by Credé and by Thiersch. He mentioned removal of the spleen in a 16 year old girl, the indication being gradual enlargement of this organ to such a size that it occupied three fourths of the abdominal cavity, causing pain and respiratory embarrassment. The patient died of hemorrhage. In the discussion of Thiersch's presentation, Langenbuch remarked that he had seen ectopy of the urinary bladder in a 75 year old man, and that he had performed operations for this condition in two 5 year old boys.

His presentations at these congresses and before the Berlin Medical Society and the ever-increasing number of his publications show his interests, the variety of cases with which he had to deal, his scientific attitude and his daring pioneer spirit. By 1882 the "Dirigierender Arzt" of the Lazaruskrankenhaus was undoubtedly a success, yet greater things were to come. Moved by the sufferings, by the futility of medical treatment, and by the loss of several of his patients with cholecystitis and cholelithiasis, Langenbuch was determined to try surgical measures. After much deliberation, animal experimentation, and studies on the cadaver, he became convinced that removal of the gallbladder would not present real technical difficulties and should lead to a permanent cure. When the occasion arose he put the matter up to the patient frankly. A few days later the patient returned, asking him to operate, and the first cholecystectomy in man was thus performed, on July 15, 1882. While such an operation seemed a daring excursion to all his contemporaries, his success proved that his preparedness more than qualified him to plan and execute such an undertaking.

In April of the following year, at the Twelfth Congress of the German Surgical Society, Langenbuch appeared with the third patient whose gallbladder he had removed successfully. He closed his presentation with the suggestion that the gallbladder should be removed not because it contains gallstones but because it forms them. His name and fame spread as others followed his steps.

A most remarkable event, and perhaps a real turning point in Langenbuch's life, was his trip to Sophia during the Balkan war. He organized and headed a voluntary medical aid expedition under the auspices of the central committee of the Red Cross. The expedition left in November, 1885, and returned in January, 1886. The story of the expedition is delightfully narrated by Langenbuch in a series of articles entitled "Kriegschirurgisches aus der Bulgarei." One seems justified in assuming that it was this service to the "Vaterland" which brought him his first official recognition: He became "Sanitätsrat."

By the time of the Eighteenth Congress (1889) of the German Surgical Society, Langenbuch had performed twenty-four cholecystectomies with results far superior to those of any of the other operative measures employed. The first volume of his "Chirurgie der Leber und Gallenblase" was published in 1894. At the Twenty-Fifth Congress (1896) Langenbuch presented a historical sketch of the development of surgery of the biliary system, an already definitely established new field in surgery. In 1897 the second volume of the "Chirurgie der Leber und Gallenblase" appeared, and with this, Langenbuch completed a lasting monument to himself.

In the "Freie Vereinigung der Chirurgen Berlins," Langenbuch was a prominent figure. He was secretary and president. At the meeting of March 11, 1901, he presided, and delivered his last address before this society. He spoke on the surgical treatment of generalized peritonitis. This was followed by a stormy discussion. On the night of June 8 and 9, 1901, Langenbuch died of generalized peritonitis following appendicitis.

Langenbuch was a stout-hearted patriot, proud of his profession, a friend of all about him, a lover of music and company, and the possessor of a deep sense of humor. He was an indefatigable, enthusiastic worker, daring, yet thorough and reliable. His presentations were always objective, to the point and dignified, yet simple and clear. He was a good physician, with much diagnostic ability, a versatile and dextrous operator who was alert, yet conservative. Langenbuch belonged to the group of surgeons who *made* modern surgery and who broadened its field with much success. From start to finish he remained the beloved "Dirigierender Arzt" of the Lazaruskrankenhaus which grew with his increasing reputation. Medical historians have yet to discover that Geheimer Sanitätsrat Professor Doctor Carl Langenbuch was one of the greatest pioneer masters of the craft and art of modern surgery.

# OSTEOMYELITIS OF THE JAWS

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NEW YORK

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## INTRODUCTION

The subject of osteomyelitis of the upper and lower jaws is very large and complicated. In this communication the general and anatomic considerations pertaining to this subject will first be discussed. Thereafter, the odontogenous origins and associations of osteomyelitis of the upper and lower jaws will be considered. Then the clinical and pathologic groupings of all cases of osteomyelitis of the upper and lower jaws will be distinguished and separated one from the other. In each of these groups the principles of the pathogenesis and pathology of osteomyelitis in general as described in previous studies will be

incorporated as they apply to each of the groups segregated, and the extraordinary phenomena associated with the various varieties of osteomyelitis of the superior and inferior maxillae will be shown to be caused by the anatomic peculiarities of the bony structures involved as well as of the vessels furnishing the blood supply of the bones in question. Lastly, certain points in differential diagnosis will be discussed, and the communication will be terminated by a résumé of the principles of treatment for osteomyelitis as they apply to lesions in the jaw bones.

This communication will include no case of tuberculous, syphilitic, actinomycotic or other generally similar type of infection.

#### REVIEW OF THE LITERATURE

There is an extensive literature on the subject of osteomyelitis of the jaws. The bulk of it is in the English, German and French languages. The largest literature is apparently in French; a number of dissertations on this subject are very extensive, but in the light of present knowledge, they do not furnish a sufficiently modern conception of this disease. The literature divides itself into four groups: One of these, the smallest, deals with osteomyelitis of the jaws proper. The second is found in the files of the dental journals and consists mostly of case reports in which the descriptions contain numerous references to osteomyelitis of the jaws usually made in a most unsatisfactory way and with inadequate or incorrect conclusions. The third deals with osteomyelitis of the jaws in nurslings and infants, of which the best descriptions are found in the German literature. A fourth group contains cases of necrosis of the jaws associated with poisoning by some of the heavy metals or with some special forms of disease as the leukemias. As it would be impossible to review adequately all of this in the space allowable for this purpose, no attempt is made to do so; references to the important communications pertaining to the subject will be made throughout this paper as the occasion arises.

The general impression one gains from reviewing all of the literature is twofold: 1. Emphasis is placed to the largest degree on the dental conditions with which osteomyelitis of the jaws is so commonly associated; however, the correct relationship of the tooth infection to the infection in the jaw bones proper is frequently not clearly stated or understood. 2. The group that occurs in nurslings and infants is more or less isolated from this general subject and is treated as if it were some independent and peculiar disease. A large literature has grown up around the subject of osteomyelitis in nurslings and infants, and, as will be pointed out subsequently, the numerous theories embodied in these numerous reports have served only to complicate the discussion. This communication will attempt, among other things, to put both of these phases of osteomyelitis of the jaws on a scientific basis.

## FREQUENCY

Osteomyelitis of the jaws is a very common ailment. The jaw bones are approximately the eighth in frequency to be affected with osteomyelitis, the order of frequency, as given by Leibold (*Journal-Lancet*, 1925), being as follows: femur, tibia, humerus, radius, ulna, vertebrae, os calcis and mandible.

Hauenstein quoted Trendel as having found involvement of the mandible 24 times and of the maxilla 4 times in 1,279 cases of osteomyelitis of all the bones.

In the last seven years (1924 to 1930, inclusive) there have been treated at Mount Sinai Hospital 450 patients with acute and chronic osteomyelitis of all kinds and of all the various bones of the body. Osteomyelitis occurred in the upper and lower jaws in 39 instances; 8 cases occurred in the upper jaw, and 29 cases occurred in the lower jaw; in 2 instances it was not clearly stated which jaw was affected. This frequency corresponds to the usual experience.

## SEX AND AGE

In the Mount Sinai series, 23 cases occurred in males as opposed to 16 cases in females. The usual ratio of males to females as given by most authorities is 3:1.

In this series the age distribution of the cases was as follows:

Up to 5 years.....	2 cases
10 to 20 years.....	9 cases
20 to 30 years.....	10 cases
30 to 40 years.....	12 cases
40 to 50 years.....	9 cases
50 to 60 years.....	2 cases

These figures refer only to hospitalized patients. In the outpatient department there are a great many more cases, and my impression is that the majority are in children.

Cases of osteomyelitis in children are no different essentially from those arising during puberty or in later life. The cases occurring in nurslings, as will be shown later, owe their peculiar clinical course merely to the anatomic location of the causative lesion, to the relatively large extent of the consequent necrosis and to the extreme youthfulness of the patient; otherwise, they are exactly similar in their pathogenesis and pathology to other cases of osteomyelitis in older children and adults. No distinction should be made, therefore, between very young children and older children, or even between children and adults. This applies with especial force to odontogenous cases. The only thing to be said is that in younger subjects the bone has more spongiosa than in older subjects or in adults, and as long as there is growth there is a

greater supply of blood and lymph; therefore, a hematogenous or odontogenous osteomyelitis may and does occur more frequently the younger the subject.

The condition occurs at all ages, not any particular age being especially liable. Osteomyelitis of a definite bacterial origin, however, is more prevalent in childhood and adolescence. In young children osteomyelitis of the upper jaw is much more frequent than that of the lower jaw, while in older children this difference no longer exists. As a matter of fact, however, ordinarily, necrosis of the lower jaw occurs oftener than that of the upper jaw because of the very much more dense bone in the lower and also because of the difference in the blood supply.

#### ANATOMY

The anatomy of the superior and inferior maxillae is well understood. A detailed description of the anatomy of the upper and lower maxillae will not be made in this communication, nor is it necessary for the purposes of this study. Suffice it to say that the superior maxilla is one of the irregular bones of the body, has intimate relations with the cavities of the mouth, the nose and the orbit, and contains within its interior one of the accessory sinuses of the nose, the antrum of Highmore.

In all of its peculiarities the superior maxilla resembles very much, both in its anatomic structure and in its biologic and physiologic characteristics, a vertebra of the spinal column. This resemblance is especially marked in relation to the subject of osteomyelitis.

The inferior maxilla, for practical purposes, consists of two long bones joined together at one extremity, the point of juncture forming in the completed structure the center of the bone and the apex of the chin. Each half, as well as the completed bone, functions structurally as a long bone. Each half is bent also at its center at a right angle to form the angle of the jaw on either side; the free extremity at either end helps to form and enters into the temporomaxillary articulation.

#### DEVELOPMENT

According to Gray, the superior maxilla commences to ossify at a very early period, and ossification proceeds with great rapidity, so that it is difficult to ascertain with certainty its precise number of centers. It appears, however, probable that it is ossified from four centers, which are deposited in membrane: one which forms that portion of the body of the bone that lies internal to the infra-orbital canal, including the floor of the orbit, the outer wall of the nasal fossa and the nasal process; a second which gives origin to that portion of the bone that lies external to the infra-orbital canal and the malar process; a third

from which are developed the palatine process posterior to Stenson's canal and the adjoining part of the nasal wall, and a fourth for the front part of the alveolus which carries the incisor teeth and corresponds to the premaxillary bone of the lower animals. These centers appear about the eighth week, and by the tenth week the three first-named centers have become fused together and the bone consists of two portions, one the maxilla proper and the other the premaxillary portion. The suture between these two portions on the palate persists till middle life, but is not to be seen on the facial surface. This is believed by Callender to be due to the fact that the front wall of the sockets of the incisor teeth is not formed by the premaxillary bone, but by an outgrowth from the facial part of the superior maxilla.

The antrum appears as a shallow groove on the inner surface of the bone at an earlier period than any of the other nasal sinuses, its development commencing about the fourth month of fetal life.

There are three stages in the development of the antrum of Highmore: (1) the formation of the anlage of the sinus inside of the cartilage capsule; (2) atrophy of the cartilage, and (3) the formation of a shell of bone around the anlage of the sinus and the beginning of secondary pneumatization. The sockets for the teeth are formed by the growing downward of two plates from the dental groove, which subsequently becomes divided by partitions jutting across from one to the other.

According to Gray's "Anatomy":

At birth and during infancy the diameter of the superior maxilla is greater in an antero-posterior than in a vertical direction. Its nasal process is long, its orbital surface is large, and its tuberosity well marked. In the adult the vertical diameter is the greater owing to the development of the alveolar process and the increase in size of the antrum. In old age the bone approaches again the character of the infantile condition: its height is diminished and after the loss of the teeth, the alveolar process is absorbed, and the lower part of the bone contracted and diminished in thickness.

According to Gray, the lower jaw is developed principally from membrane and partly from cartilage. The process of ossification commences early—earlier than in any other bone except the clavicle. The greater part of the bone is formed from a center of ossification (dentary), which appears between the fifth and sixth week in the membrane on the outer surface of Meckel's cartilage. A second center (splenial) appears in the membrane on the inner surface of the cartilage, and from this center the inner wall of the sockets of the teeth is formed; this terminates above in the lingula. The anterior extremity of Meckel's cartilage becomes ossified, forming the body of the bone on each side of the symphysis. Two supplemental patches of cartilage appear at the condyle and at the angle, in each of which a center of ossification for these



parts appears; the coronoid process is also ossified from a separate center. At birth the bone consists of two halves, united by a fibrous symphysis, in which ossification takes place during the first year.

Further anatomic facts and details will be found in their appropriate places throughout the subsequent parts of this communication.

#### ODONTOGENOUS CONSIDERATIONS

Osteomyelitis of the upper and lower jaws is intimately associated with the subject of caries of the teeth, of tooth infection and of certain traumatic conditions of the teeth, and knowledge of the related odon-

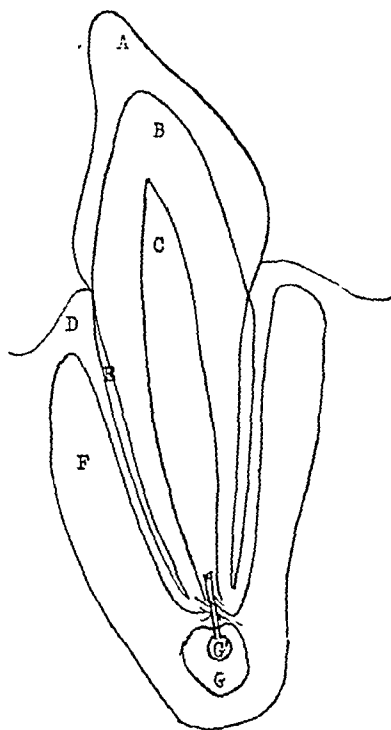


Fig. 1.—Structure of a typical tooth. *A* indicates the enamel; *B*, the dentin; *C*, the pulp and pulp cavity; *D*, the dental periosteum; *E*, the cement; *F*, the bone; *G*, the canal in the bone carrying the nutrient artery, and *G'*, the nutrient artery with an apical branch. (After Gray's Anatomy.)

togenous conditions is necessary for a proper understanding of the subject of osteomyelitis of the jaws.

The surgical anatomy of a typical tooth, as given in Gray's Anatomy, is as follows:

A longitudinal section of a tooth will show the presence of a central cavity corresponding in a general way to the crown of the tooth. Processes of the main chamber pass from its body, one down into each root, each one opening at the apex by a minute orifice, the apical foramen. This cavity is known as the pulp chamber; the minute canals, the pulp canals. The cavity contains a soft, vascular and sensitive organ called the dental pulp. It is made up of myxomatous tissues and contains

numerous blood vessels and nerves, which enter by way of the apical foramina. It does not possess lymphatics. The periphery of the pulp is bounded by a layer of cells arranged like columnar epithelium, each cell sending one or more branched process through the basic substance of the dentin. These are the dentin-forming cells, the odontoblasts of Waldeyer. The blood vessels break up into innumerable capillary loops, which lie beneath the layer of odontoblasts. The nerve fibrils break up into numberless nonmedullary filaments, which spread out beneath the odontoblasts, and probably send terminal filaments to the extreme periphery of the pulp outside the odontoblasts.

The matrix cells and their processes are irregularly arranged in the body of the pulp, but in the canal portion the fibrillae are in the direction of the axis of the root.

Section of the tooth will exhibit three hard tissues in a tooth: one forming the greater mass of the tooth; hence its name dentin (the ivory); a layer that covers the exposed part of the dentin in the crown of the tooth, the enamel, and a thin layer, which is disposed on the surface of the fang, the cement or *crusta petrosa*; the cementum and enamel are thinnest at the neck and thickest on their distal portions.

The ivory, or dentin, forms the principal mass of a tooth; in its central part is the cavity enclosing the pulp. It is a modification of osseous tissue, from which it differs, however, in structure. On microscopic examination it is seen to consist of a number of minute wavy and branching tubes having distinct parietes. They are called the dentinal tubuli, and are embedded in a dense homogeneous substance, the intertubular tissue.

The enamel is the hardest and most compact part of a tooth, and forms a thin crust over the exposed part of the crown, as far as the commencement of the root. It is thickest on the grinding surface of the crown until worn away by attrition, and becomes thinner toward the neck. It consists of a congeries of minute hexagonal rods, columns, or prisms. They lie parallel with one another, resting by one extremity upon the dentin, which presents a number of minute depressions for their reception, and forming the free surface of the crown by the other extremity.

. . . Numerous minute interstices intervene between the enamel fibers near their dentinal surface. It is noted in rare cases that the dentinal fibers penetrate a certain distance between the rods of the enamel. No nutritive canals exist in the enamel.

The cortical substance or cementum (*crusta petrosa*) is disposed as a thin layer on the roots of the teeth, from the termination of the enamel as far as the apex of the root, where it is usually very thick. In structure and chemical composition it resembles bone. It contains, sparingly, the lacunae and canaliculi which characterize true bone; the lacunae placed near the surface receive the canaliculi radiating from the side of the lacunae toward the periodontal membrane, dental periosteum; and those more deeply placed join with adjacent dentinal tubuli. In the thicker portions of the *crusta petrosa*, the lamellae and Haversian canals peculiar to bone are also occasionally found.

Odontogenous conditions fall into the following groups:

*Superficial Caries of the Teeth.*—Caries of the teeth begins in the nooks and crannies furnished by the irregularities of the crowns (i. e., the exposed portions) of the teeth. Particles of food gather there; ever present organisms—molds, fungi and streptococci of various strains—find a good haven for growth; the superficial enamel and the underlying dentin soften and gradually become eroded by attrition; a superficial cavity results. Pain is present only when the nerve endings are exposed.

As long as the pulp cavity is not entered, the integrity of the tooth is not diminished. No involvement of the jaw bone proper ever occurs with this variety of tooth condition.

*Involvement of the Pulp Cavity and Root Canal.*—The pathology of the dental pulp has been most completely studied by Wedl, Slater and Black, and nearly all of the knowledge now possessed on this subject has come as a result of their researches. The available knowledge indicates that there are two distinctive varieties:

1. Bacterial infection is often a source of acute hyperemia of the pulp. This is commonly caused by the invasion of the pulp chamber by the disintegrating processes of caries originating as described in the immediately preceding section. It, however, not infrequently occurs in those cases in which the pulp has not been exposed, but is still covered with a layer of decalcified and softened dentin (pseudo-exposure), the tubuli of which are filled with saprophytic and pyogenic organisms that readily penetrate to the pulp and establish irritation, inflammation, supuration and devitalization. A thin layer of sound dentin is a positive external protection against the infection of the pulp with the pyogenic organisms.

When secondary involvement of the capillary vascular loops in the pulp cavity takes place, a much more heightened process results during the course of which the tooth structure disintegrates much more quickly. Periapical abscess formation frequently forms a part of the picture. Usually a cystic cavity results involving more than one apical area.

In a general way, superficial caries of the teeth is followed by extension of the process into the root canal and corresponds in its mechanism to direct infection of bone tissue in general following some form of trauma, as I have described in previous communications. Naturally, in exposed structures such as the teeth, trauma need be of a relatively minimal kind such as would ordinarily accompany the grinding of one tooth on another in the mastication of food. A severer trauma accompanies the biting of hard food material (the cracking of nuts), and frequently results in the breaking away of segments of the crown of the teeth. The further progression of the infection along paths produced by an eroding process parallels the further progression of an osteomyelitis of any bone under similar conditions.

2. Suppurative conditions can establish themselves in the pulp cavity and root canal without direct external infection. The presence of pyogenic organisms in the blood current, which may have gained an entrance through some abrasion of the skin or mucous membrane, or through a wound or preexisting abscess, according to Marshall, has long been recognized. These are capable, when they become arrested in a blood vessel, of rapidly propagating and of establishing suppurative

conditions. This explains the presence of abscesses of the pulp that are occasionally found in apparently perfectly sound teeth. Such dormant abscesses may not present any acute symptoms until they are opened, when, if the utmost aseptic precautions are not observed, they sometimes undergo most violent exacerbations of the inflammatory processes, which may terminate in the loss of the tooth and in extreme cases in establishing a fatal general blood infection.

The pathologic picture described in the previous paragraph corresponds accurately with the conception of the origin and pathogenesis of acute osteomyelitis of the bones of the skeleton that I have described and discussed in previous communications. Such infection of the teeth is indeed a metastatic infection.

The further development of these odontogenous conditions leads one into the subject of dento-alveolar abscess. It is found that all cases of dental infection can be grouped somewhere along this biologic development. The discussion of the subject of dento-alveolar abscess follows presently.

*Pyorrhea Alveolaris*.—Pyorrhea alveolaris seems to be an essentially different condition. A wide difference of opinion exists in reference to the etiology of this disease. Marshall has found, after a careful review of the literature, that the opinions can all be grouped under four heads:

1. That the disease originates in some constitutional state or dyscrasia.
2. That the disease is caused entirely by local irritation and environment.
3. That the disease is due to the infection of the tissues with micro-organisms.
4. That the disease is induced by deficient exercise of the teeth, gums and alveolar process.

Pyorrhea alveolaris primarily affects the pericementum, manifesting itself in a suppurative inflammation, sometimes acute in form, but generally of a chronic type; secondarily, the inflammatory process involves the walls of the alveolus and the gum. The gum retracts from the side of the tooth; the potential space between the root and the tooth socket becomes an actual interval as the infective and irritative process spreads downward into the socket; coincidentally, the tooth loosens in the socket and the blood supply of the tooth becomes impaired; finally, the blood supply is entirely destroyed, and a "dead" tooth results. The process is accompanied by a discharge of pus from the alveolus, and by a gradual disintegration of the alveolar process (caries); finally, the tooth loses its alveolar and gingival connection and falls out.

On the loss of the tooth, the inflammatory symptoms immediately subside, a circumstance that, according to Marshall, lends great weight to

the theory that the local manifestations of the disease are primarily associated with the dental tissues, and not with the gingivae or the alveolar processes. Witzel and others have maintained, however, that the disease is primarily located in the alveolar border, and that the gum and pericementum are involved as a secondary feature of the disease.

*Fracture Cases.*—Quite commonly with fracture and other injury of the jaws fractures also occur in the teeth. Usually the crown is broken away, and the root remains embedded in its socket. If allowed to remain, the root dies and infection takes place.

*Dento-Alveolar Abscess.*—An important item in the development of osteomyelitic foci of either of the jaws is the suppuration that occurs. In this regard all odontogenous considerations are of maximum importance. Suppuration about the teeth arising from purely dental origins is a common occurrence. The following are the important facts to be remembered from the dental point of view in considering the subject of osteomyelitis of the jaws.

In dental practice the term dento-alveolar abscess includes any accumulation of pus within a dental alveolus, or associated therewith. An acute and a chronic form of dento-alveolar abscess are described. In the acute form the symptoms are often severe, with marked local and general constitutional manifestations. Extensive necrosis of the jaw bone proper and sloughing and gangrene of the soft tissues are frequent complications, and cases are on record in which a general blood infection ensued with an eventful fatality.

*Bacillus pulpaepyogenes* of Miller is, according to Marshall, generally thought to be the organism responsible for the establishment of an acute dento-alveolar abscess. It is found in decomposing and gangrenous pulps and in putrescent root canals. It is exceedingly virulent. White mice, when inoculated with it by the peritoneal route, die in from eighteen to twenty hours.

A chronic dento-alveolar abscess may be the sequel of an acute abscess that has established a fistula. A slowly developing chronic abscess also forms in the absence of any fistula formation; these are the so-called blind abscesses. These conditions, if untreated, may persist for months or years without causing any alarming objective symptoms. When a fistula exists there is, generally, a constant discharge of pus into the mouth. In both varieties of abscess the predominant micro-organism present is usually *Streptococcus viridans*. This is the organism that, according to Billings, Rosenow, Hartzell and others, seems to be the chief factor in the production of so many of the diseases that are now classified under the generic term of "focal infection."

In the chronic form of abscess the symptoms are usually much milder than in the acute variety, and there may even be a relative absence of

symptoms as far as the local region is concerned. Rarely exacerbations of infection occur with secondary involvement and necrosis of bone and with the local and general manifestations of a local or general infection exactly as in the acute variety.

Most of the dento-alveolar abscesses either belong to the variety commonly called periapical abscess or result as a further development of a periapical abscess. Periapical abscess is an accumulation of pus about the apex of the root of a tooth and results in the following ways:

(a) In one variety, a periapical abscess results from the mechanism by which involvement of the pulp cavity and root canal occurs following an initial superficial caries, as described in the previous sections.

(b) A periapical abscess forms after trauma that results in fracture of a tooth, especially when the line of fracture passes through the root; also after an operative trauma during which fragments of instruments have been broken off and left in the pulp or root canals. A nonvital tooth results and leads to the formation of the periapical abscess.

(c) A periapical abscess is frequently found in the alveoli of vital teeth, as, for instance, in pyorrhea alveolaris and in inflammatory conditions arising from various forms of irritation and traumatism of the pericementum.

(d) In the absence of other demonstrable pathologic changes (traumatic or otherwise) in the given tooth, a periapical abscess represents, in my opinion, a metastatic infection following a pathogenesis similar to that in ordinary types of osteomyelitis of other bones. The establishment of the given point of fixation depends on minor traumas incident to the grinding and mastication of food, and the inflammatory process centers in the vascular channels present in the depths of the socket from which the nutrient artery of the tooth is derived. A relatively circumscribed lesion results marked by erosion of the tip of the root and of the adjacent walls of the tooth socket, and by the formation of a minute abscess cavity lined by a granulation membrane. The bacteriologic content of the abscess is the streptococcus.

Another form of dento-alveolar abscess is one that has no external sinus for the discharge of the pus. These cases have been for this reason designated as blind abscesses. The term is, however, hardly a correct one, for the pus discharges through the pulp canal, which becomes its sinus, and it is therefore not a blind abscess. These abscesses are usually small, and, as a rule, are not very painful; in fact, all of the acute symptoms are greatly modified by reason of the ready exit of the pus from the beginning of the suppurative process. A blind periapical abscess of this variety has a good many similarities to the chronic type of bone abscess found in the long bones, which was first described by Brodie.

## CLINICAL GROUPING OF CASES OF OSTEOMYELITIS OF THE JAW

*Cases With and Without Odontogenous Factors.*—A number of clinical groups and subgroups can be distinguished as the cases of osteomyelitis of the jaws present themselves. Theoretically, the distinctions are easily made; in actual practice, however, the groups are not always so easily definable, and the proper integration of an individual case is frequently a matter of difficulty. In each of these groups one commonly finds: (1) Cases in which odontogenous factors can be definitely excluded, and (2) those in which odontogenous factors play a distinct rôle and must be included.

This phase of the study will properly be appropriately included as it applies in the discussion of each of the previous groups. In actual practice, the classification of any given case is made difficult because of any odontogenous association. According to the mechanism involved, one can distinguish:

Primary cases.

Extension cases.

Hematogenous cases.

**Primary Cases:** Osteomyelitis of the jaws, in contradistinction to osteomyelitis of the other bones of the skeleton, is quite frequently a primary process and does not depend on hematogenous infection. Direct infection of the bone tissue occurs only through the intermediation of some trauma. In accordance with the manner of application of the trauma, three groups can be distinguished:

Civil injuries—falls, blows, etc.

Gunshot wounds, including those in civil life as well as in military practice.

Osteomyelitis following operative manipulations, wiring of fractures, excision of tumors, cysts, etc.

Gunshot wounds form a class by themselves and will not be discussed in this communication. The essential difference between gunshot wounds in civil life and during a military emergency lies in the depleted and exhausted condition of troops on the battle-line and in the enormous increase in environmental contamination (usually of a fecal nature) incident to active warfare in the field.

Osteomyelitis following operative manipulation results from an exposure of bone tissue, or from the opening of vascular channels leading into the bone tissue, or as a result of operatively produced or postoperative spontaneous frank fractures that result from the removal and consequent weakening of the bone structure. This variety follows the course usually seen in the ordinary civil form of injury to the jaws followed by infection of the bone tissue.

Odontogenous factors enter in primary cases of osteomyelitis of the jaws when the effects of the primary trauma include the breaking away

of portions of the crowns of the teeth, or when the line of fracture of the jaw passes simultaneously through the roots or sockets of the teeth. A devitalization of the given tooth or teeth follows immediately, and dental surgeons have learned to extract such teeth immediately in order to obviate any subsequent trouble, at least as far as the dental factor is concerned. This precautionary procedure immediately removes this element of the discussion.

Infection of the bone following the ordinary form of trauma sustained in civil life occurs because of the presence of a compound fracture of the jaw. The line of communication with the exterior, in the vast majority of the cases, leads into the interior of the mouth through a rent in the mucous membrane. Contamination and infection occur immediately, and the degree of the contamination and the resulting infection seems uncontrollable by any means at command, as it is impossible (1) to cleanse and to perform débridement of the wound properly, (2) to close the wound in the mucous membrane adequately and (3) to prevent the continuous introduction of additional infection.

The essential pathologic changes include the introduction of infection into the opened vascular channels (thrombophlebitis), beginning in the plane, and on either side, of the line of fracture. The amount of pathologic change and its intensity depend (1) on the kind and virulence of the infecting organism and of its opposing antibody formation, (2) on the amount of disturbance of blood circulation and (3) on the character and degree of the consequent deprivation of food supply from the bone cells. The last item determines the amount of bone necrosis. There is a tremendous variation in the amount of necrosis that follows. In those fortunate cases in which the anatomic position of the fragments is such as to encourage free drainage and in which, also, secondary thrombosis and blockage of the blood stream do not reach into a blood vessel of sufficient size, the number of bone cells that die and the amount of bone that becomes devitalized are absolutely or relatively small or entirely absent, and the wound heals by granulation with minimal, or without any, sequestration. When the opposite condition prevails and a major trunk becomes thrombosed, relatively large amounts of bone sequester. Between the two extremes, naturally, the latitude of variation is infinite. In my own experience, I have met with examples of all kinds, from those in which no bone at all is sequestered to those in which sequestrums measuring several inches in their largest diameters have subsequently been discharged from the sinuses, or have been removed at operation. Usually, however, the amount of bone tissue that sequesters is relatively small and represents a marginal necrosis at the line of fracture. Suppuration either does not occur or is of minimal extent. In all respects the pathologic picture is similar to that in cases of osteomyelitis of the long bones complicating a compound



fracture in which the focus develops in the vascular network, as described elsewhere. Depending on the size and importance of the vascular channel that is thrombosed and on the abundance of the collateral circulation, little or no bone necroses or larger segments become involved and finally sequestrate.

**Extension Cases:** Most of the cases of osteomyelitis of the jaws should be classified as extension cases. By that I mean that the osseous lesion is due to the spontaneous extension of the infection along vascular channels into the jaw bones from an area of infection in close proximity with the bone. The subgroups are as follows:

1. Extension from a lesion in the attached soft parts.
2. Extension from a lesion in the gum.
3. Extension of odontogenous origin.
4. Extension after operative manipulation.
  - (a) After dental operations.
  - (b) After surgical operations on the jaws.
  - (c) After dental manipulations, including the use of carbolic acid or of arsenic.

1. This group includes cases in which osteomyelitis of the jaw—and here it is practically invariably the lower jaw—has resulted from an extension of an inflammatory focus in the soft parts clothing the bone. The number of cases in this group is comparatively and actually very small.

A few cases have been reported in which staphylococcus infections of the chin have progressed sufficiently deeply to involve the underlying lower jaw. This has been the point of view of most of the observers. While Herrath expressed the belief that ordinarily this is a hematogenous infection, he, nevertheless, acknowledged that the extension mechanism is extremely possible in diabetic and other similar subjects.

2. Hauenstein quoted Williger, who reported a case of chronic osteomyelitis of the lower jaw that resulted from an ulcer of the gum in the region of the molar teeth.

The extension mechanism for osteomyelitis of the jaw in cases of this kind is dependent on the character of the vascular supply. The characteristics to be described are applicable to the lower jaw almost entirely and explain the reason why extension cases are almost invariably in association with the lower jaw. The blood supply of the lower jaw, as indicated elsewhere, consists of the nutrient (inferior dental) artery and of the periosteal circulation derived from contiguous muscular and other arterial trunks. The latter supply is very abundant, and individual vessels must necessarily be implicated from time to time when inflammatory lesions in the soft parts clothing the bone are appropriately placed. That such vessels will undergo thrombosis is

obviously to be expected, and an extension of the infection along the thrombosed vessels follows as a matter of course. Should such an infected thrombotic process spread inward sufficiently far to enter within the confines of the jaw, an osteomyelitis results, and any compromisation of blood supply is evidenced by a corresponding necrosis and sequestration.

I remember seeing this sequence of events on one occasion in the upper jaw:

A man approximately 60 years of age came to the hospital with a gangrenous process involving the gum covering the posterior extremity of the upper alveolar process. When the slough began to separate, it was found that bare necrotic bone underlay it. After several weeks, a large sequestrum separated spontaneously. There was no other definite etiology to be determined for the bone necrosis.

I explain this pathologic picture on the following anatomic and pathologic grounds: The gangrenous process in the gum, because of its position, involved the gingival branch of the posterior dental artery (hence the gangrenous character of the process). Thrombosis of this vessel occurred as a matter of course. Extension of the thrombotic process occurred in a retrograde manner into the trunk of the posterior dental artery. Necrosis of that portion of the alveolar process followed as a result of the deprivation of the blood supply, and resulted in the discarded sequestrum.

3. Cases of odontogenous origin are, of course, the commonest examples of the extension group. Nevertheless, spontaneous extension of the infection from a diseased tooth into the bone tissue of the jaw is comparatively uncommon. Anatomically, this would indicate that the pathologic process had extended in a retrograde fashion by a progression of the thrombosis into one or more of the larger branches, or into the main trunk of the dental artery (superior or inferior, depending on which jaw was involved), and had led to compromisation of the blood supply and consequent necrosis and sequestration.

4. The cases that follow some operative (usually dental) trauma form the largest number of the cases in the extension group seen in ordinary practice. The dental manipulation or operation may be performed in cases in any of the groups considered in the section devoted to odontogenous considerations of the subject, and the operative procedure varies from the cleaning out and repair by filling of the cavities, to tooth extraction and possibly other manipulations. The usual clinical history includes the general and local symptoms associated with focal infection of one kind or another, or a frank toothache, a visit to the dentist during which an extraction is usually done and an almost immediate onset of pain in, and a swelling of, the jaw, accompanied by chill, fever and other constitutional manifestations of a bacterial infec-

tion of more or less virulence. The history frequently includes one or several additional operations during which additional incisions were made along the gums, or externally, with little or, more usually, no relief; a characteristic manifestation is an exaggeration of the objective symptoms each time these additional incisions are made. Finally, roentgen studies show the presence of sequestrating bone, and the diagnosis is established, if not suspected before that time.

The preexisting lesion in and from which the exacerbation and spreading of the infection originate is a variety of dental infection; frequently some variety of dento-alveolar abscess is present, usually the simple periapical abscess. Such cases are undoubtedly due to the mechanical spreading of infection along newly opened planes and their transmission into healthy vascular channels of the cortex and interior of the jaw bones. Secondary vascular thrombosis is always present, and the extent of this determines the amount of devitalization and the extent of consequent necrosis of bone.

Another extension type of necrosis of the jaw of odontogenous origin, which used to be seen many years ago, is that which followed the injection of carbolic acid or the use of arsenic. This practice has been wisely given up by practically all dentists.

I have the records of one case in which the injection was done for the relief of pain. Extreme pain and swelling followed immediately, and after a very stormy time in which necrosis of almost the entire alveolar process of the upper jaw resulted, a sequestrum was extracted by operation, and healing ensued in a very slow manner.

Blair and Brown reported the following case:

In a woman, aged 32, some arsenic was left in a tooth for two weeks. There was a local abscess; many teeth became loose, and there was widespread necrosis of the jaw. Several teeth extractions and sequestrotomies were necessary.

**Hematogenous Cases:** The mechanism of the pathogenesis and pathology of hematogenous osteomyelitis in general has been discussed extensively on a number of previous occasions, and an extensive discussion of this subject will not be repeated here. Suffice it to say in résumé:

Acute hematogenous osteomyelitis is a metastatic lesion that develops during the course of bacteremia, the latter resulting from an acute bacterial lesion on a surface of the body that forms the portal of entry for the infection. In this conception, a surface of the body includes not only the skin, but also the entire mucous membrane of the alimentary tract, the genito-urinary tract, etc. The common surface lesions include not only furuncles, carbuncles, etc., on the skin, but also easily demonstrable lesions in the tonsils, and in other lymphadenoid collections lying in the mucous membrane of the pharynx, as well as less demonstrable lesions, such as those in Peyer's patches.

~~XX~~ The fundamental cause of the spreading of the original lesion in the form of metastatic or subsidiary lesions is an infected thrombus lying in the original area of infection, and communicating at some point with the freely circulating blood. The organisms growing on the surfaces of the thrombus are discharged, or pieces of the thrombus itself break off and are discharged into the circulation, and, becoming lodged for various reasons in the vascular network of various parts of the body, give rise to secondary lesions. Bone tissue, because of its peculiarities in vascular structure, seems particularly prone to the blocking of these thrombi-emboli, and the susceptibility to this condition is particularly increased during the period of growth when the individual bones contain well marked hyperemic areas at the junction of the diaphysis and epiphysis, around centers of ossification, etc.

The various accessory causes, such as trauma, that determine the localization of a secondary focus of infection—fixation point—in a given bone are associated with accidents in the local circulation which facilitate blocking of any bacterial thrombus-embolus. ~~XX~~

Mengel described a case of osteomyelitis of the upper jaw with secondary empyema of the antrum, which followed trauma to the root of the nose. Lichtwitz has also noted osteomyelitis following trauma to the side of the face. In this instance, the antrum was not affected.

~~XX~~ The essential nature of the pathologic process that develops at the fixation point is a thrombo-arteritis or thrombophlebitis, and the process in the vertebrae is exactly similar to that in other bones in which a dominating position is assumed by the secondary vascular thromboses that must necessarily occur in such a pathologic lesion. The all-important secondary effects that these thromboses produce are disturbances of essential nutrition, which lead to the death of certain bone cells, and the consequent necrosis of certain areas of bone tissue.

Proof that a hematogenous origin for an osteomyelitic lesion of the jaw occurs is furnished by the relatively abundant occurrence of cases of osteomyelitis during the course of infectious disease, especially when specific organisms such as typhoid or influenza bacilli play the etiologic rôle, and by the occurrence of chronic bone abscesses in the jaw. Cases also occur ordinarily when the character of the bacteriology, i. e., the finding of *Staphylococcus aureus*, makes it strongly suggestive that the lesion in the jaw is of blood borne origin. ~~XX~~

According to Marshall, hematogenous infection of the teeth also occurs; a differentiation as far as the odontogenous considerations are concerned is attempted by Marshall on the following basis:

When the symptoms are first noted immediately after the treatment of a quiescent nonvital tooth this rather suggests a preexisting periapical streptococcus infection which may have been present for years. When such an infection involves a tooth with intact walls it must be considered as being of blood-borne origin.

In actual practice, hematogenous cases are seen by the dentist as the periapical variety of dento-alveolar abscess easily distinguishable on the criteria presented by Marshall. The surgeon seldom sees hematogenous cases of osteomyelitis of the jaws with such clearcut etiology. Usually by the time the patient comes for treatment the lesion is so extensive that it apparently implicates the tooth and the jaw, and it becomes impossible to evaluate cause and effect except on certain circumstantial evidence, such as (1) the presence of a suggestive or specific bacteriology, (2) the association with an acute infectious disease or (3) certain clearcut forms of pathology as, for instance, a bone abscess buried deep in the bone tissue and isolated from the adjacent teeth. In most instances the dental pathology seems to dominate the picture, and it is usually assumed that the latter is the cause of the entire lesion, whereas,

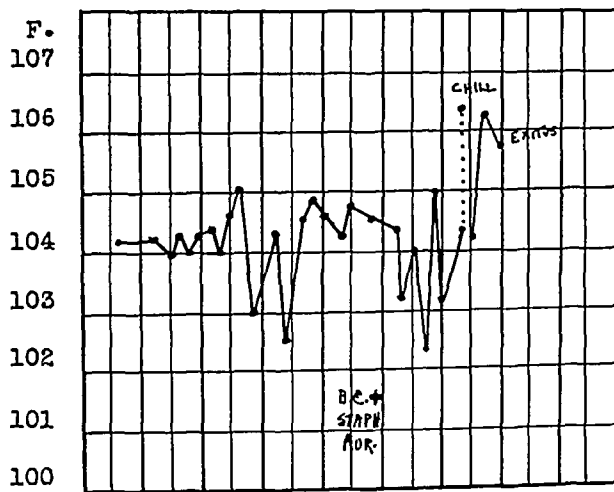


Fig. 2.—Temperature chart.

as a matter of fact, it is possible for a hematogenous infection to form points of fixation (1) either in the teeth or in the jaw, with subsequent extension of the infection from either one to the other; (2) in both the teeth and the jaw simultaneously, or (3) in both the teeth and the jaw at subsequent times with coalescence of the foci into a seemingly single lesion. The following case is illustrative.

An 8 year old boy was admitted to the hospital with an alveolar abscess of the left mandible following the extraction of a tooth performed several days before admission. The temperature on admission was 104 F., and the patient appeared very toxic. There was marked swelling over the left side of the jaw, but no point of fluctuation. As shown in figure 2, the temperature fluctuated between 103 and 105 F. In spite of apparent local improvement, the general condition became worse. Ten days later, the patient complained of pain in the right elbow, and a metastatic focus was found in the lower end of the humerus and was opened. Again there was improvement, but again the patient became toxic and went into a state of stupor and coma. Cultivation of the blood showed *Staphylococcus aureus*. The patient died two days later.

The clinical picture resembled accurately that seen in cases of sepsis associated with the ordinary form of acute osteomyelitis.

Hematogenous infection of the tissue of the jaw occurs in association with the following conditions:

1. Osteomyelitis following the ordinary local form of infection.
2. Osteomyelitis following or coincident with infectious diseases.
3. Osteomyelitis in nurslings and infants.
4. Osteomyelitis in adults with unerupted teeth.
5. Chronic bone abscess of the jaw.

1. Osteomyelitis following the ordinary local form of infection. Cases of osteomyelitis of the jaws following foci of infection, such as furuncles, etc., as with other bones of the skeleton, are relatively and actually rare. Perthes classified the commonest infecting organisms as the staphylococci.

2. Osteomyelitis following or coincident with infectious diseases. The mechanism and pathogenesis of cases of osteomyelitis of the jaws that arise in the course of an acute infectious disease are similar to those that occur as hematogenous infections of bone elsewhere and under ordinary conditions. The position of the jaws in the mouth and the necessity for cleansing and other manipulations of the mouth make these bones particularly prone to traumatism of all kinds and to carious conditions around the teeth. While in possibly a very few cases the osteomyelitis of the jaw may conceivably be a direct extension from an ulcerative stomatitis or other generally similar condition, the traumatism that are demonstrable are more probably agents in determining the localizations than primary portals of entry for the infection. The assumption seems all the more probable because specific bacteria, for example, typhoid or influenza bacilli, etc., are found in the bone.

The important infectious diseases that can be complicated by osteomyelitis of the jaws include typhoid fever, influenza, measles and scarlet fever. There are such reports in the literature by Mantell, Schmiegelow, Heath, Patissier, Gagliardi, Salter, Layton, Albanese and others. Less often it occurs after chickenpox, smallpox, diphtheria and typhus fever. The type in the exanthematic cases may be bilateral, as in a case described by Cadenat and Cola.

According to Perthes, cases are most common in association with typhoid fever and influenza. Cases of typhoid fever have been reported by Perthes, Albanese, Burkett and others.

(a) According to Salter and others, cases of osteomyelitis of the jaws are most common after scarlet fever. In the official reports of the Metropolitan Asylums Board (which controls all the fever hospitals of London) for 1897, Mantell described 19 cases of necrosis of the

jaw in a series of 12,230 cases of scarlet fever. In 16 of these there was a common factor determining the necrosis, viz., mechanical injury. The throat and mouth were, of necessity, frequently cleansed, and food was given at frequent intervals; the patients actively resisted this treatment. The necrosis began in the height of the acute stage, close to the symphysis of the lower jaw. Seven of the 16 patients died. In only 3 was the upper jaw involved, and of these 2 recovered. In those days syringing the throat was a common method of treatment, and to do this the gag was frequently needed in a recalcitrant child. Of the 3 other cases, 1 was a case of general ulcerative stomatitis occurring in the fourth week and ending in death. The 2 others were associated with alveolar abscesses around a carious tooth.

(b) Two cases were reported by Layton in 1928. In his report he referred to the fact that cases had rarely been seen after smallpox. In some of these cases necrosis of the jaw resulted in communications with the antrum; a pansinusitis was also present.

The osteomyelitis of smallpox divides itself into two distinct groups. The first, a rather infrequent complication, is the suppurative type, which occurs as a result of secondary infection. The second is due to the variola itself, occurs during the course of the disease and has all the histologic characteristics of the typical smallpox lesion. This type of osteomyelitis is nonsuppurative and resembles closely the lesions found in orchitis variolosa. Chiari, in 1892, described osteomyelitis variolosa in detail. In a large number of necropsies on patients with smallpox, he found necrotic foci widely distributed through the bone marrow of the long bones, and, in a few cases, in the sternum and vertebrae. The lesions were found as early as two days and as late as two months after the appearance of the eruption, without any evidence of suppuration, even in the late cases. Although he found this condition in 86 per cent of the cases he examined, there are very few clinical case reports.

In 1910 and 1913, Musgrave and Sison reported 20 cases of marked bone deformities in adults from whom they obtained a history of smallpox in childhood. The fact that the bone disturbance began to manifest itself first during the course of the attack of variola, together with the work of Chiari, led them to believe that this was the etiologic factor. From the character of the deformity—a shortening of the long bones with no disturbance in circumferential growth—they inferred that the site of the disease was either in the epiphysis or in the area of growth. Since then there have been several other cases reported.

(c) A case of osteomyelitis of the jaw with complete necrosis was reported by Patissier to have occurred in a soldier during the course of typhus fever. This seems to be extremely rare.

3. Osteomyelitis in nurslings and infants.<sup>1</sup> A considerable literature has grown up around the cases of osteomyelitis of the upper and lower jaws that is found to occur in nurslings and infants. The first case reported in the British literature was by Douglas, in 1898; in the American literature, by Posey, in 1912. Since then numerous communications have appeared in the literature of the various continental and American countries.

Practically all writers agree that the disease must be of bacterial origin, but there is considerable controversy as to whether or not it is a primary lesion of the jaw bone, a minority believing that it is a hematogenous infection of the jaw. The majority believe that it is a primary infection of the bone, the portal of entry being somewhere along the gum, in the teeth buds, the nose or the antrum, aided and localized by various forms of trauma during childbirth or thereafter.

The available sources for the infecting organisms are (1) the vaginal canal of the mother, (2) the fingers of the accoucheur or the nurse, (3) the nipples and breasts of the mother and (4) the fingers or apparatus employed in cleansing the baby's mouth.

Pathologically, the brunt of the infection centers in the entire jaw bone, much more often in the upper than in the lower. Usually, the entire bone seems to be involved almost at once, and the process exhibits itself either simultaneously or in quick succession on the palatal, nasal and orbital aspects of the bone in the form of abscesses; the teeth are quickly exfoliated, a discharge appears from the nose, and an orbital abscess forms. Necrosis and sequestration of the jaw bone follow.

In explaining this pathologic picture, the various writers have attempted to find origins for this extensive process in a primary process in the nose, in the unerupted teeth buds (Kleming, in the Koerner Clinic) or in the antrum of Highmore (Paunz, of Budapest).

My own impression and belief are that osteomyelitis of this type occurring in nurslings and infants is in no way different from the hematogenous form of osteomyelitis in general occurring in other parts of the body, and that the occurrence of the lesion in such young subjects is associated with the physical conditions of childbirth and the environmental conditions immediately following. The localization in the jaws is, as is held by almost everybody, due to various forms of minor or major injury received during childbirth or to various forms of trauma received thereafter associated with the care of the child, especially with cleansing of the mouth. The predilection of the upper jaw is due to its larger size and its more rigid construction and attachment in the skull, which favor the more frequent reception of traumatism.

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1. An extensive discussion of this group of cases of acute osteomyelitis of the jaw in nurslings will be made in another communication.



The presence of unerupted teeth and teeth germs or buds determines areas of more marked vascularity, which help to determine points of fixation for the metastatic infection. The traumas described as occurring on the alveolar border or elsewhere, which are taken to be the primary points of entry for the infection, should not be assumed to make pathways directly to the bone; these traumas favor the formation of a *locus minoris resistentiae*. The transmission into the substance of the jaws is made possible by way of the blood stream and not by simple extension by contiguity.

The actual pathogenesis and pathology are exactly similar to those in other cases of hematogenous osteomyelitis. The point of fixation in the vascular channels of either of the jaws develops into a thrombophlebitis. The occlusion of the vascular channels results in the usual deprivation of blood supply and nourishment, and the amount, degree and character of the resultant necrosis are in direct proportion to the number, size or importance of the vascular channels occluded and the amount of available collateral circulation (see section on "Bone Necrosis in Osteomyelitis of the Jaws," p. 215).

The controversy as to whether or not this form of osteomyelitis of the jaw centers and is derived from a lesion in the teeth buds, the nose or the antrum is to my mind unnecessary and fruitless, as, from the facts outlined, one can easily see that all of these manifestations are simply determined by the dominating position of the thrombophlebitis in the course of the vascular channels described. The seeming importance of any one manifestation is only superficial, and the character of the pathogenesis and pathology is, as in other forms of acute osteomyelitis, intimately related to the position of the thrombophlebitis and the resultant necrosis.

The disease presents a clearcut, definite, clinical picture, one case report being similar to the others. Usually in a healthy infant a few weeks old, unidentifiable prodromal symptoms are followed by high fever, vomiting and prostration. A swelling then appears, beginning in the cheek or the infra-orbital region, and almost always there is edema of the lower eyelid. The sclera is inflamed, a conjunctivitis is present, chemosis is sometimes noticed, and not uncommonly some exophthalmos is present. An abscess forms in the swelling. Similar swellings and abscess formations form on the palate or alveolus in the mouth, and teeth buds exfoliate through the resultant fistulas. A purulent discharge escapes from the nose, which seems to be connected with the swelling in the cheek. All of this occurs in a very few days. The temperature continues irregularly, convulsions are frequent, and there are marked anorexia and difficulty in nursing. The outcome is healing with or without the persistence of sinuses, the development of metastatic

purulent foci or the infant dies as a result of the virulence of the infection, either before or after secondary foci appear.

The mortality is large, varying from 25 to 50 per cent in the various series of cases reported in the literature. The final result, when the infant lives, is a considerable deformity of the face and palate, with loss of the teeth, both temporary and permanent, on the side involved.

The differential diagnosis is to be made between this form of osteomyelitis and the following conditions:

1. Ophthalmia neonatorum. This is usually a bilateral lesion, and gonococci can be demonstrated.
2. Erysipelas.
3. Dacryocystitis.
4. Syphilis.
5. Tuberculosis.

Careful examinations usually clear up the diagnosis.

4. Osteomyelitis in adults with unerupted teeth. I have seen patients with osteomyelitis of the jaw—usually the lower jaw—with typical sequestration of portions of the alveolar processes or of the bodies of the bone in whom roentgen studies demonstrated an unerupted tooth buried deeply in the bone tissue. The initial stages of the local condition are not accompanied by any apparent tooth infection, although, invariably, such an assumption is made, as the patient interprets the pain as “toothache.” Indeed, in one of my cases the erupted teeth at the locality of the process were missing. No wound or other traumatic condition of the gum is present. The clinical course includes the usual manifestations up to and including the sequestration, the separation and the exfoliation of the necrotic portions of the jaw. Subsequent closure of the wound or fistula does not, however, occur until the unerupted tooth is removed at operation.

I interpret the sequence of events as follows: A hematogenous infection takes place in the bone tissue surrounding the cavity of the unerupted tooth, the latter possibly forming the determining factor for the point of fixation; interference with the food supply of the unerupted tooth is a secondary phenomenon resulting from the compromise of the vascular channels of that portion of the jaw bone itself involved in the inflammatory process; the unerupted tooth then acts as a foreign body and prevents the healing of the wound until it is removed.

5. Chronic bone abscess of the jaw. In 1858, Nussbaum described a bone abscess of the left side of the lower jaw in a 21 year old woman. Frankel, Herzog (1889), O. Faisst Kuhn, Weise and many others have also described similar cases. I have, personally, never encountered such a case. It is a curious fact that these reported cases have occurred



in the lower jaw. It is impossible for bone abscesses of this type to form in the interior of any bone, unless on a hematogenous basis.

It is a nice point for discussion, whether or not a hematogenous periapical abscess of the teeth should not more correctly be classified as a chronic bone abscess of the jaw. As indicated previously, the blood supply of the individual teeth is furnished by terminal arteries, branches of the corresponding dental artery, which perforate the fangs of the teeth at their apices and penetrate the pulp cavity of the teeth (fig. 1). A thrombo-embolic process that became centered in these terminal branches would result in a small abscess immediately surrounding the vessel, which, because of the very nature of the anatomic arrangement, would be situated around the apex of the fang of the tooth; hence the name, periapical abscess. The association of this variety of dento-alveolar abscess with dental practice has apparently been determined because of the proximity of the teeth, whereas, in truth, it might more correctly be classified with diseases of the jaw.

#### SUPPURATION WITH OSTEOMYELITIS OF THE JAWS

Knowledge of the forms and varieties of suppuration about an osteomyelitic focus in either of the jaws is important from the point of view of surgical treatment, and in this regard a complete understanding of the odontogenous factors is necessary. It appears that when a tooth is the seat of an acute dento-alveolar abscess, there is always a considerable involvement of the bony structure at the apex of the root. The pus is at first confined to the apical space, where it is surrounded by bony walls. As the pus accumulates, a disintegration of the surrounding cancellated bone takes place, and a gradually increasing cavity is formed around the apex of the root. Such disintegration should, however, not be classified as a form of osteomyelitis of the jaw unless secondary involvement with destruction of bone cells can be demonstrated in the jaw bone proper as a result of thrombophlebitic involvement of the vascular channels in the bone.

As the external or buccal wall of the alveolar process is the thinnest, it offers the least resistance to the progress of the constantly accumulating pus; for this reason the abscess usually burrows through the external plate in its further development and points on the buccal aspect of the alveolar process opposite the apex of the root. Dento-alveolar abscesses can, however, point in the following other ways after penetrating the bony walls of the tooth socket:

-  1. Directly through the soft tissues.  Dento-alveolar abscesses that point directly through the gum tissues are the most common, and rarely present any complications. Many of these are the common gum-boils.

~~2.~~ 2. By separating the periosteum from the bone and forming a secondary pus pocket.

3. By following the pericementum along the side of the root and discharging at the margin of the gum. ~~These~~ These abscesses are sometimes confounded with the so-called blind abscesses, but in these cases a careful examination will reveal the fact that there is no discharge through the pulp canal. Many times this form of abscess is associated with pulpless teeth, the roots of which have been filled, but in which there is sufficient bacterial irritation to keep up a chronic discharge of pus through the sinus that has been formed by the side of the root.

~~4.~~ 4. Occasionally, pointing toward the tongue.

5. Through the floor of the nasal fossa. ~~The~~ The relations of the roots of the incisor and cuspid teeth to the floor of the nose are such, in many instances, that appropriately placed dento-alveolar abscesses may point through the floor of the nasal fossa and produce a purulent discharge that might readily be mistaken for chronic nasal catarrh. The relations of the roots of the bicuspid and molar teeth to the floor of the antrum are such as to make it even less difficult for an abscess connected with one of these teeth to penetrate the floor of the sinus.

~~Clinically~~ Clinically, as soon as the pus penetrates the bony walls of the abscess and escapes into the soft tissues, the severity of the pain is abated, but the tissues begin immediately to swell, and sometimes the swelling is very great. When the abscess is associated with the upper jaw, it not infrequently closes the eye. When located in the lower jaw, in the region of the molars, it may be so extensive as to make deglutition impossible, and greatly obstruct breathing. This condition is sometimes erroneously diagnosed as Ludwig's angina. ~~XX~~

Acute dento-alveolar abscesses rarely heal spontaneously; there is, however, a partial filling up of the pus cavity by the growth of granulation tissue. But there is usually a sufficient amount of decomposition of tissue and growth of micro-organisms within the abscess cavity and the pulp canal to keep up the suppurative process.

Occasionally, a dento-alveolar abscess may present chronic symptoms from the very beginning of the suppurative process, as, for instance, in blind abscesses. There are often a prolonged and obstinate irritation at the apical space and a persistent accumulation of pus, which finds an exit through the pulp canal, and the toxins of which are taken up and absorbed by the blood current or the lymphatic stream. These abscesses are among the most dangerous to the general health of the patient, as they are fruitful sources of general sepsis. Teeth so affected, which do not respond to treatment after a fair trial, should be extracted.

Abscesses that have pointed through the external tissues of the face are nearly always of a chronic type, particularly those that have had

their origin in ancient traumatism, perforation of the cementum, broken instruments within the root canal or from an impacted position of a tooth.

I think it should be assumed in cases of osteomyelitis of the jaws associated with odontogenous factors that any suppuration beyond the simplest forms should be ascribed to the associated lesion in the jaw bone. In going through the various dental contributions, it is worthy to note how frequently the suppurations described are said to be complicated by necrosis of portions of the jaw bones. Any suggestion of necrosis of the jaw should, of course, remove such suppuration from the category of dental to that of the jaw bone osteomyelitis proper, even though the shedding of a sequestrum is not always necessary to prove the involvement of bone, because these are essentially subperiosteal abscesses that are not always associated with necrotic bone.

The character and localization of any suppuration derived from an osteomyelitis of the jaws are determined by the anatomic contour of the bones, and by the attachment of muscle tendon and fascial planes. (A) The common locations of abscesses derived from osteomyelitis of the upper jaw are (see section on "Treatment," p. 225) as follows:

1. In the maxilla, the commonest location is in the cheek. The abscess spreads upward and outward toward the orbit and the zygoma. The subcutaneous tissues are very loosely applied to the underlying bone, and an abscess of considerable size develops.

Abscesses that gather in the cheek have a tendency to be accompanied by much necrosis of the subcutaneous tissue of the cheek. I believe that this has some relation to a thrombo-embolic lesion of the posterior alveolar gingival and buccal arteries which supplies the tissues of the cheek as well as the alveolus (fig. 3).

2. As has been described (see section on "Osteomyelitis in nurslings and infants," p. 203), abscesses develop also in relation to the nasal, palatal and orbital surfaces of the upper jaw.

(a) The abscesses pointing into the nose never attain a large size before they rupture spontaneously; as a matter of fact, these localizations are commonly not recognized clinically until they do rupture. Anatomically, the nasal localizations of the abscess are related to branches of the anterior dental artery and to the branches of the nasopalatine artery that supplies the nasal surface of the superior maxilla.

A case of localization of the osteomyelitic process on the nasal surface of the maxilla with secondary empyema of the antrum was reported by Menzel.

A 21 year old man sustained an injury of the root of nose. Quite soon thereafter he fell ill with pain in the region of the frontal sinus, and there seemed to be involvement of the orbit. There were high fever and other signs of a general infection. After one week a discharge of pus and blood occurred from the nose, and

the subjective symptoms disappeared. The discharge of pus continued. Bone necrosis was suspected, and at the operation it was determined that necrosis of the nasal wall of the antrum had occurred. The frontal sinus manifestations were due to involvement of the duct in the inflammatory process.

(b) Abscesses accumulating on the palate are derived naturally from the palate process of the maxilla and are related to lesions in the palatal vessels. They are seen most frequently in nurslings and infants. They are usually subperiosteal abscesses.

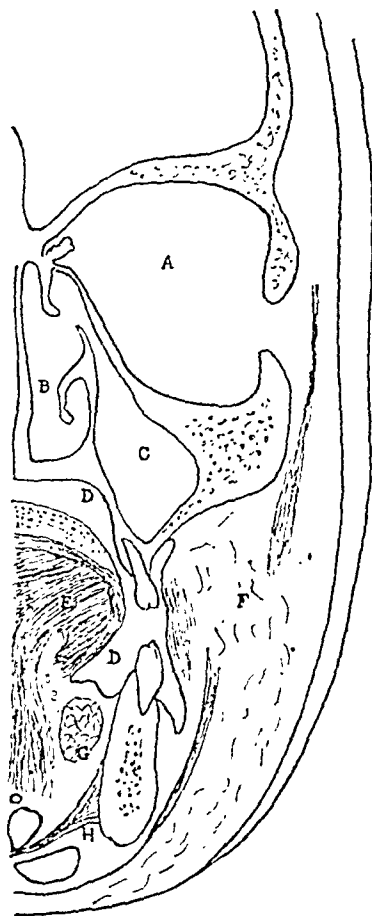


Fig. 3.—Cross-section to show the relationship of the alveolar arches and the contiguous cavities and areas. *A* indicates the orbit; *B*, the nasal cavity; *C*, the antrum; *D*, the oral cavity; *E*, the tongue; *F*, the cheek; *G*, the floor of the mouth; and *H*, the submaxillary triangle. (From the Manual of Surgical Anatomy, Medical Departments, United States Army and Navy, 1918.)

(c) Pus that accumulates on the orbital surface of the upper jaw forms an orbital abscess that quickly causes marked chemosis, induration and swelling of the orbital fat with protrusion of the eyeball and fixation and closure of the lids. Spontaneous rupture commonly occurs in the area contiguous to the inner canthus. In the further development of the abscess, the suppuration extends upward to the roof of the orbit.

The anatomic basis for the orbital localization of the bone lesion and its consequent suppuration is a lesion in the infra-orbital artery as it lies in the floor of the orbit (i. e., the orbital surface of the superior maxilla).

In nurslings and infants, all three of these localizations commonly occur simultaneously.

3. A group of cases occurs in which the suppuration extends into the antrum of Highmore, and an empyema of the latter cavity occurs (figs. 3 and 4).

The antrum of Highmore, or maxillary sinus, is a large pyramidal cavity in the interior of the maxillary bone. Its walls are everywhere exceedingly thin, and correspond to the orbital, facial and zygomatic surfaces of the body of the bone. Its inner wall contains a large irregular aperture, which communicates with the middle meatus of the nasal fossa. The posterior dental canals, transmitting the posterior dental vessels and nerves to the teeth, are on the posterior wall. Several conical processes, corresponding to the roots of the first and second molar teeth, project into the floor of the antrum; in some cases, the floor is perforated by the teeth in this situation. The antrum is lined by a continuation of the mucoperiosteum, which covers the surfaces of the nasal fossa and its accessory sinuses. The anatomic basis for involvement of the antrum is usually a lesion in the posterior alveolar and posterior dental arteries so placed that the necrosis of the alveolus which subsequently occurs includes the lower and outer angle of the bony wall of the antrum. The antrum becomes infected by contiguity. Commonly, the physical characteristic of such a lesion is a peculiar gangrenous infection of the upper jaw, which results in the sequestration of such a large segment of the alveolar process and body of the upper jaw that the antrum is laid wide open.

I have the records of two cases of this kind.

A man, approximately 45 years of age, who had a history of prolonged and profound indulgence in alcohol and other excesses, complained of toothache that seemed to be caused by an infected tooth. Very quickly a foul odor became apparent, and a gangrenous process developed in the surrounding tissues, which quickly acquired a line of demarcation. No definite, extraordinary, etiologic cause (poisoning by heavy metals, leukemia, etc.) was demonstrable. When the dead tissue was removed at operation, one could look into a large hole, the apex of which was the antrum of Highmore. In spite of the fact that the dead tissue was removed at the earliest possible moment, the general condition of the patient became progressively worse, and he died.

In a man, approximately 60 years of age, an infection developed around one of the lateral teeth of the upper jaw. An abscess formed. The tissues thereafter assumed a gangrenous appearance, and the general condition of the patient deteriorated. There was a high fever. During one of the dressings, when an attempt was made to pull away some of the gangrenous tissue, a large segment of

the alveolus came away with it. The resulting cavity had for its apex the cavity of the antrum of Highmore. There was a tedious convalescence, but healing eventually occurred by epithelization of the cavity. At the time of the patient's discharge from the hospital, there was a good deal of discomfort and disability while eating, because of this cavity, and the latter was therefore later occluded by a hard rubber obturator.

An empyema of the antrum of Highmore can also occur as a complication of a periapical abscess surrounding the roots of the appropriate

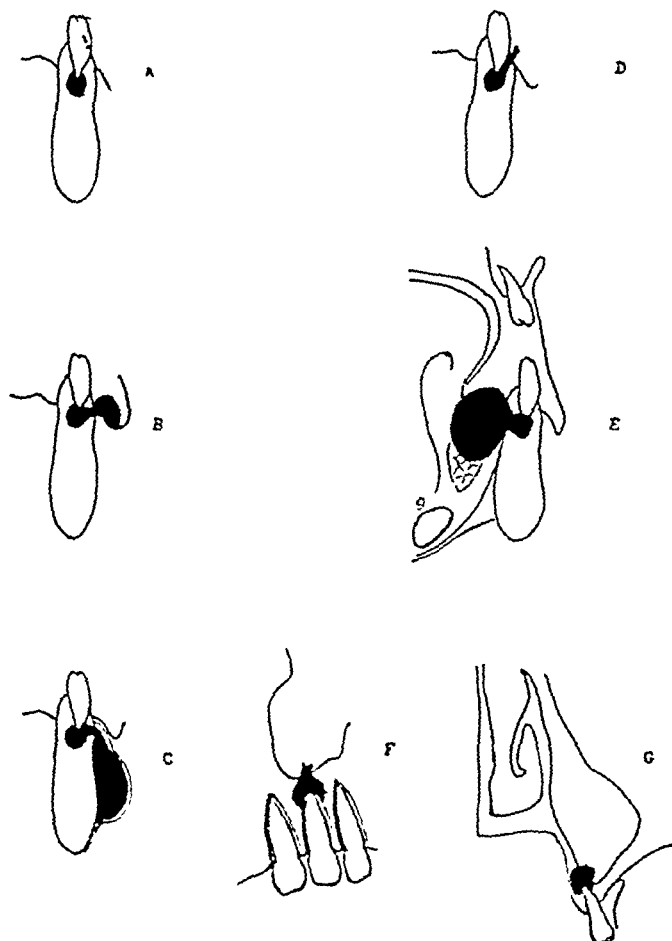


Fig. 4.—To show the lines of spread of a periapical abscess. *A* indicates a periapical abscess; *B*, a direct spread, gumboil type; *C*, a secondary "subperiosteal" type of pus pocket; *D*, follows pericementum and escapes at margin of gum; *E*, toward the tongue and in the floor of the mouth; *F*, points into the nasal cavity; *G*, perforates into the antrum.

teeth (fig. 4). Marshall and others also agreed that the anatomic basis of this lesion is a thrombo-embolic lesion of the apical arteries, the terminal branches of the superior dental artery as they enter to supply the substance of the teeth (fig. 1). In clinical practice, the differentiation is frequently impossible. Luckily, this is of no particular moment, because the line of treatment is the same.



Secondary involvement of the bone, originating in a sinusitis complicated by an empyema of the antrum of Highmore was observed by Lubet-Barbon and Furet. As a good deal of operating had been done, it is questionable whether the bone necrosis was not secondary to the operative manipulations rather than to the primary sinusitis.

4. A case of localization of the suppuration in the antrum, secondary to bone necrosis in the outer wall (canine fossa) of the maxilla, was reported by Halloran.

5. Cases are described in which the suppuration gathers behind the maxilla and extends upward as far as the base of the skull.

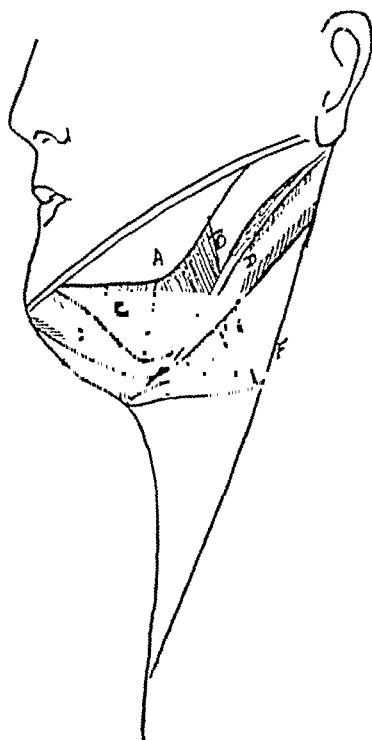


Fig. 5.—This shows the relationships of the lower jaw (*A*) to the mylohyoid muscle (*B*), the hyoglossus muscle (*C*), the digastric muscle (*D*), the hyoid bone (*E*) and the margin of the sternomastoid muscle (*F*). (After Gray.)

(*B*) Abscesses in relation to the lower jaw find the following general localizations:

6. On the outer side of the bone, they appear either in the interval between the cheek and the alveolus as gum-boils or larger abscesses, or, in relation to any part of the external surface of the bone—body or ramus—they burrow outward to localize in the subcutaneous tissue covering the lower jaw. Care is necessary in opening these abscesses not to injure the facial artery.

7. On the inner side of the lower jaw (fig. 5), the pus accumulates most commonly below the line of attachment of the mylohyoid muscle,

and the abscesses point in the submaxillary triangle. They should be opened externally. Less commonly the pus accumulates above the line of attachment of the mylohyoid muscle, and the abscess is then situated in the floor of the mouth to one side of the base of the tongue. These abscesses should be opened through the floor of the mouth.

8. Suppuration derived from an osteomyelitis of the angle of the jaw and in relation to the sockets of the last molar teeth usually burrows outward and points in the neck just below the angle of the jaw. If not opened soon enough, the abscesses spread forward around the posterior margin and in front of the mylohyoid muscle, and extend into the submaxillary triangle. Very occasionally, the abscess spreads further. If the spread occurs in front of the pretracheal fascia and anterior to the coalescence of the latter with the fascial investment of the great vessels (carotid sheath), the pus spreads downward in the anterior triangle of

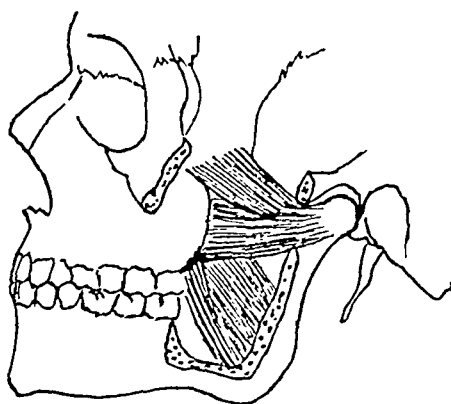


Fig. 6.—To show the origins and insertions of the external and internal pterygoid muscles and their relationship to the spread of any accumulations of pus. (After Gray.)

the neck, and may rupture or be incised and drained at any point above the clavicle. According to Marshall, cases are on record in which abscesses have discharged into the larynx and at points on the chest as low as the breasts.

9. Abscesses in relation to the ascending ramus of the lower jaw (fig. 6), on its inner aspect internally and anterior to the attachment of the pterygoid muscles point into the interior of the mouth far back and high up. Usually the inflammatory swelling is sufficient to ankylose the jaw more or less, and because of this fact the abscess is difficult to reach for the purposes of incision. The abscess usually breaks spontaneously into the oral cavity, and if one can find the opening, bare bone is invariably felt at the bottom of the sinus. Thereafter, the ankylosis, when due merely to inflammatory exudation, subsides slowly until full mobility is restored. Ankylosis, however, that is due to any calcification

in muscle or tendon, or to any new bone formation, is usually much more difficult to treat; full defervescence does not always occur, and complete ankylosis occasionally results.

On the inner aspect of the ascending ramus, pus that accumulates behind and to the outer side of the pterygoid muscles at their attachment to the lower jaw points in the interval behind the posterior margin of the jaw.

Pus that accumulates on the outer surface of the ascending ramus presents most of the physical characteristics of a parotid abscess. In incising the abscess, great care is necessary not to injure the branches of the facial nerve.

Large accumulations of pus are the rule with osteomyelitis of the lower jaw. These most frequently have the physical and anatomic characteristics of subperiosteal abscesses. As mentioned before (*vide supra*), sequestration does not always accompany these subperiosteal abscesses, although it quite commonly does. The anatomic relationships of the soft parts clothing the lower jaw of the muscles and their tendinous attachments, and of the planes of the various layers of the cervical fasciae, determine the path of spread of the accumulations of pus.

According to Gray, the cervical fascia consists of three layers: (1) a superficial layer, (2) a layer passing in front of the trachea, and forming with the superficial layer a sheath for the depressors of the hyoid bone and (3) a prevertebral layer passing in front of the bodies of the cervical vertebrae, and forming with the second layer a space in which are contained the trachea, esophagus, etc. The superficial layer forms a complete investment for the neck. It is attached behind to the ligamentum nuchae and the spine of the seventh cervical vertebra; above it is attached to the external occipital protuberance, to the superior curved line of the occiput, to the mastoid process, to the zygoma and to the lower jaw; below it is attached to the manubrium sterni, the clavicle, the acromion process and the spine of the scapula; in front it blends with the fascia of the opposite side. This layer would oppose the extension of abscesses toward the surface, and pus gathering beneath it would have a tendency to extend laterally. If the pus is in the posterior triangle, it might extend backward under the trapezius muscle; it might extend forward, under the sternocleidomastoid muscle; downward, it might extend under the clavicle for some distance, until stopped by the coalescence of the cervical fascia to the costocoracoid membrane. If the pus is contained in the anterior triangle, it might find its way into the thorax to become continuous with the pericardium; but, owing to the lesser density and thickness of the fascia in this situation, it more frequently finds its way through it and points above the sternum. The second layer of fascia

is connected above with the hyoid bone. It passes down beneath the depressors and in front of the thyroid body and trachea to become continuous with the fibrous layer of the pericardium. Laterally, it invests the great vessels of the neck and is connected with the superficial layer beneath the sternocleidomastoid muscle. Pus forming beneath this layer would in all probability find its way into the posterior mediastinum. The third layer (the prevertebral fascia) is connected above to the base of the skull.

#### BONE NECROSIS IN OSTEOMYELITIS OF THE JAWS

The physical characteristics of the area of bone necrosis that accompanies and follows osteomyelitis of the jaws, as in other bones of the body, vary directly with the size and importance of the vessel or vessels occluded by the osteomyelitic process.

(A) The blood supply of the superior maxilla is very abundant and is furnished by a number of moderately large vessels (the infra-orbital, the alveolar, the descending palatine, the sphenopalatine, the ethmoidal, the frontal, the nasal and the external maxillary vessels). Practically all of these vessels are derived from the trunk of the internal maxillary artery. The anastomosis is very free, and none of the arteries functions as an end-artery. The various aspects and areas of the maxilla that are supplied by the various vessels are fairly accurately indicated by their descriptive names. Practically the entire segment of the alveolar process is supplied by the alveolar branch of the internal maxillary artery and its continuation as the posterior dental artery.

A periosteal network is practically nonexistent; the little that corresponds to this is derived from an abundant network in the mucous membrane covering the alveolar process of the bone. The physiologic proof of this deficiency is found in the total absence of any new bone formation after disease or destruction of any part of the bone.

The interesting part of the blood vessel arrangement for the superior maxilla is found in the dominating fact that the entire supply is derived from one large arterial trunk, the internal maxillary artery, and that the branches enumerated previously, which form the network of supply, are arranged in loops based on the trunk of the internal maxillary artery. Study of figure 7 will amply demonstrate this fact. As an example, note the loop formed by the infra-orbital artery and the posterior dental artery by the interposition of the anterior dental branch of the former; or the loops formed by the gingival branch of the posterior dental artery with the nasal branch of the infra-orbital. It is as if a series of loops had their free ends gathered in a single bundle corresponding to the main trunk of the internal maxillary artery.

This simple anatomic fact explains adequately all the clinical forms of bone involvement and of bone necrosis that are found in osteomyelitis of the upper jaw, as follows:

1. Involvement of the entire bone with manifestations referable to the palatal, nasal and orbital surfaces results from a lesion in the stem of the internal maxillary artery prior to the giving off of the posterior alveolar branch with or without extension thrombosis in the loops described, which are derived from the internal maxillary artery. Collateral circulation is at a minimum, and a maximum lesion results.

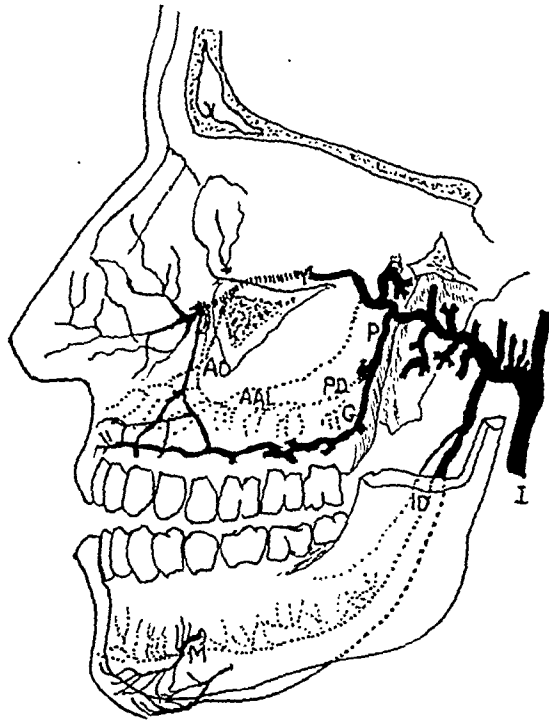


Fig. 7.—The blood supply of the superior maxilla. (After Deaver's Anatomy.) Study of this figure shows that the entire blood supply of the maxilla is derived from one large arterial trunk, the internal maxillary artery, and that the branches supplying the bone consist of, and are arranged as a number of, loops thrown around the bone at different levels and in different planes. For example, note the loop formed by the infra-orbital branch and the posterior dental branch by the interposition of the anterior dental branch of the former, etc. *I* indicates the internal maxillary artery; *P*, the posterior alveolar artery; *PD*, the posterior dental artery; *G*, the gingival branch of the posterior dental artery; *AD*, the anterior dental artery; *AAL*, the vascular loop from which the apical arteries are derived; *ID*, the inferior dental with its apical branches; *M*, the mental branch of the inferior dental artery.

2. Involvement of the alveolar process results from a lesion in the course of the posterior dental and gingival arteries. The amount of bone involved depends on the amount of collateral circulation.

3. Involvement of the anterior part of the alveolar process and the adjacent part of the bone results from a lesion in the course of the junction of the posterior and anterior dental arteries.

Involvement of the antrum of Highmore occurs with either group 2 or 3. The amount of bone involvement depends on the possibilities of collateral circulation.

4. Involvement of the palatal surface results from a lesion in the palatal arteries, or may be an extension from an involvement of the alveolar process.

5. Involvement of the nasal aspects of the bone results from a lesion in the nasal and anterior branches of the infra-orbital artery. This variety may also be associated with an empyema of the antrum of Highmore.

6. Involvement of the orbital aspect of the bone results from a lesion in the course of the infra-orbital artery.

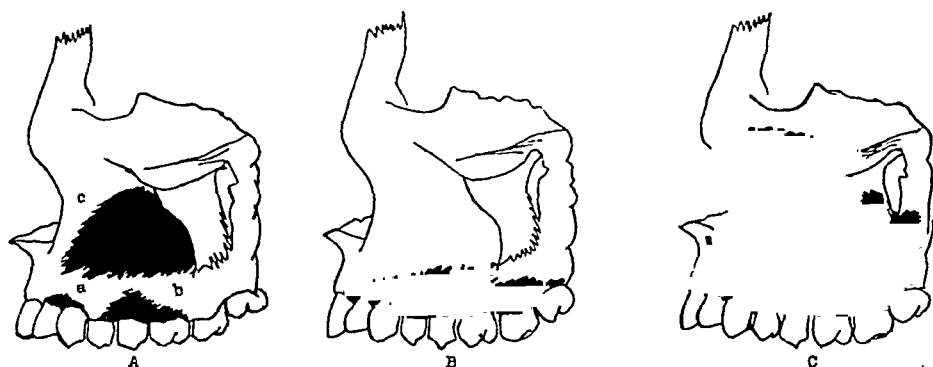


Fig. 8.—To show some characteristic sequestrums that form from the superior maxilla. (See text.)

Sequestration in the superior maxilla corresponds to these areas of involvement and occurs in the following anatomic forms:

1. The usual sequestrums derived from the superior maxilla are small and of little or no importance, and ordinarily consist of small fragments from the margin of the teeth sockets, or larger segments extending more or less through the thickness of the socket and the alveolar process (fig. 8 A, a and b).

2. A characteristic sequestrum is found in the group described as occurring in nurslings and infants. The sequestrum involves practically the entire maxilla. The basis for this is anatomic (figs. 7 and 8 C).

Necrosis of the entire maxilla could be explained only on the presence of a lesion in the main stem of the internal maxillary artery prior to its division into the infra-orbital and posterior alveolar branches.

3. A sequestrum is seen which consists of the major portion of, or the entire, alveolar process, the separation or removal of which results

in laying bare the cavity of the antrum of Highmore. The anatomic basis for this must consist in a lesion (thrombo-embolic vascular occlusion) of the main trunk of the alveolar branch of the internal maxillary artery before its division into its component branches (fig. 8 *B*).

4. Rarely, the area of necrosis is limited to the nasal aspect of the maxilla (Menzel). The anatomic basis for this is a lesion in the branches of the anterior dental artery.

5. Rarely, the area of necrosis is limited to the outer side of the bone in the area contiguous to the zygoma (Halloran).

A case of this type occurred in a 60 year old man in whom an empyema of the antrum with high fever and an extensive cellulitis of the face developed, which compelled incision. Bare bone was felt in the canine fossa, and the finger broke through (fig. 8 *A, c*) easily into the antrum, demonstrating necrotic bone over a wide area extending backward and upward toward the root of the zygoma.

The anatomic basis for this type of sequestrum is a lesion in the appropriate branches of the infra-orbital branch of the internal maxillary artery.

Characteristic case reports are found elsewhere in this communication.

(*B*) The vascular arrangement for the inferior maxilla is as follows (fig. 7): The inferior dental artery penetrates the foramen on the inner side of the ramus of the jaw, and runs along the dental canal in the substance of the bone. Opposite the first bicuspid tooth it divides into two branches, incisor and mental; the former is continued forward beneath the incisor teeth as far as the symphysis, where it anastomoses with the artery of the opposite side; the mental branch escapes at the mental foramen, and anastomoses with the submental inferior labial and inferior coronary arteries. The dental and incisor arteries, during their course through the substance of the bone, give off a few twigs that are lost in the cancellous tissue, and a series of branches that corresponds in number to the roots of the teeth; these branches enter the minute apertures at the extremities of the fangs and supply the pulp of the teeth.

Collateral circulation is furnished from the opposite artery, and by its mental branch with the submental, inferior labial and inferior coronary arteries.

For my purpose this description may be paraphrased as follows: Each inferior dental artery acts as a nutrient artery for its appropriate half of the bone; it perforates the substance of the bone on the inner surface of the ascending ramus of its appropriate side, divides dichotomously and nourishes the bone up to the upper ends of the rami; in fact, the two inferior dental arteries are the nutrient arteries of the inferior maxilla. The upper ends of the rami are supplied from adjacent muscular branches.

The periosteal circulation is derived from numerous arterial trunks—muscular and otherwise—in the immediate neighborhood; it is most abundant over all parts of the bone except the upper part of the ascending ramus and its coronoid and condyloid processes. Here the periosteal structure disappears in the intimate rugged attachment of muscles, tendons and ligaments.

Sequestration of bone in the mandible as a result of osteomyelitis is characterized by being relatively small or grossly large (fig. 9).

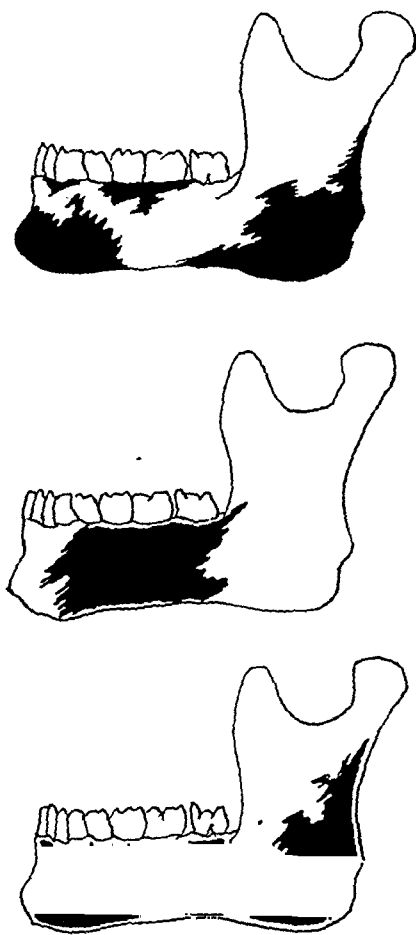


Fig. 9.—Types of sequestrums that form from the mandible.

Small and insignificant sequestrums limited to the margins of the teeth sockets are naturally common. Equally common, if not more so, are the large sequestrums that occupy relatively large extents of the mandible; these can be grouped as follows:

1. A variety in which the sequestrum occupies a large or major part of the body of the mandible.
2. A variety in which the sequestrum occupies the angle of the jaw and extends therefrom forward along the lower border of the mandible



and upward along the posterior margin of the ramus for a limited extent.

3. A variety in which the sequestrum is present at the point of the chin, usually displaying a tendency to extend more to one side than to the other.

4. A variety in which the entire body of the mandible forms the sequestrum; this includes the body, angle and lowermost parts of the ramus. Very rarely, this extends across the middle line and involves the opposite side.

The anatomic basis for these forms of sequestration is found in either the extension (odontogenous) or the metastatic (hematogenous) form of thrombo-embolic process in the inferior dental artery. The extent of bone deprived of blood supply by this process depends on the length of artery involved in the process, on the position of the diseased portion, with especial reference to its nearness or distance to the next nearest large anastomosing vessel (the inferior dental of the opposite side and the incisor and mental branches), and on the amount of collateral circulation. Because of the position of these anastomosing branches, blocking of the artery at any point proximal to these branches converts the artery into an end-artery, with all of its consequences up to the point of blockage.

The vascular arrangement for the upper half of the ascending rami of the mandible is as follows:

The coronoid and condyloid processes and the contiguous part of the ramus are supplied with blood by a number of arterial branches derived, for the most part, from the internal maxillary artery. This blood supply has very little collateral anastomosis with the blood supply of the remainder of the mandible, as represented by the blood supply derived from the inferior dental arteries.

Sequestration of the coronoid or condyloid processes of the ramus is uncommon. This probably has some relation to the great frequency of odontogenous factors in the production of osteomyelitis of the body of the lower jaw.

#### NEW BONE FORMATION IN OSTEOMYELITIS OF THE JAWS

As in other bones of the skeleton, the formation of new bone is an important element in the final healing and cicatrization of the bone wounds. New bone formation here, as in other bones of the body, is dependent to the largest extent on the presence of, and the anatomic structure of, the periosteum. As in both the upper and the lower jaw there is no true marrow cavity, any new bone formation derived from any endosteal osteoblastic cells is lacking.

(A) A small area on the anterior surface of the superior maxilla just below and in front of the malar process has a covering that approaches in structure that of a periosteal membrane. The membrane is continuous over the inferior orbital margin with the periosteum covering the floor of the orbit. The palatal surface and the alveolar process are covered with a thick mucoperiosteal membrane. The other surfaces of the bone are covered with the relatively dense attachment of muscles and tendons that find anchorage deep in the bone tissue, and in this respect the structure resembles that of the vertebrae. No periosteal membrane is present on these latter surfaces.

The important function of bone production under proper stimulus seems lacking in the upper jaw. Deficiencies of bone produced by disease, or otherwise, are not made good by bone tissue, but are repaired as best as nature may by ordinary fibrous tissue. Wherever the disease, by necrosis and sequestration, aided or not by operative removal of sequestrums, has resulted in the opening up of any accessory cavity such as the antrum, the defect remains; and either the latter is repaired by the coalescence of mucous membranes across the bared areas, or, as frequently happens, no covering takes place and the bared bone persists. At no time in clinical practice does one ever see the formation of involucrum at any point of the upper jaw. Repair in the sense of new bone production does not apparently exist.

(B) The lower jaw is clothed by a distinct periosteum at all parts except near and over the condylar and coronoid processes. Here the periosteal membrane becomes incorporated with the tendinous attachments of muscles and the fibrous structure of the ligaments of the temporomaxillary articulation. The periosteal circulation derives itself from numerous vessels in the immediate vicinity, is very abundant and furnishes the physical and physiologic basis for the involucrum, which forms under appropriate conditions about the lower jaw.

This faculty of bone production is well developed, and involucrum formation is abundant over all parts of the mandible except the upper parts of the ramus and its condylar and coronoid processes. In the latter locations, that is, in the neighborhood of the temporomaxillary articulation, a calcification occurs very commonly in the adjacent parts of the tendons and muscles attached to the coronoid and condylar processes; this should not be mistaken for the formation of new bone tissue.

#### COMPLICATIONS OF OSTEOMYELITIS OF THE JAWS

*Lymphatic Drainage as a Complication of Osteomyelitis of the Jaws.*  
—The cervical lymphatic glands frequently become swollen and tender, and commonly suppuration takes place in them. Schweitzer has

described the lymphatic drainage of both the lower and the upper jaw. This is best summarized in the attached table taken from his paper.

*The Association of General Infection (Bacteremia, Sepsis, Septicemia) with Acute Osteomyelitis of the Jaws.*—In osteomyelitis of the jaws, the clinical signs of a general infection may occur (*A*) at the onset of the illness or (*B*) later on, either as part of the essential pathology of the bone lesion or as part of some complicating condition.

(*A*) In the early cases it is most uncommon for the manifestation of the general infection to assume a dominant position, either immediately preceding or simultaneously with the onset of the local manifestations except in cases in which the hematogenous mechanism is well marked; such dominance occurs under the following conditions:

(*a*) In cases of specific infection, as in cases of typhoid, osteomyelitis of the jaw, etc., the general infection confines itself to the

*Regional Drainage of Lymph Vessels of Upper and Lower Jaws*

From the Region of	Upper Jaw Into Submaxillary Glands			Lower Jaw Into Submaxillary Glands		
	Ant.	Med.	Post.	Ant.	Med.	Post.
Incisors and canines	Only exceptionally one vessel	Almost $\frac{1}{6}$	Almost $\frac{1}{6}$	About $\frac{1}{3}$	About $\frac{1}{2}$	Occasionally
Premolars.....	0	Almost $\frac{2}{3}$	Almost $\frac{1}{3}$	Rarely	Almost all	0
Molars.....	0	Almost $\frac{1}{2}$	A little more than $\frac{1}{2}$	Occasionally 1 vessel	Almost all	Occasionally 1 vessel

characteristics it displays as a manifestation of the original illness, for instance, the typhoid fever. It is very uncommon for the general infection to assume the characteristics of a fulminating sepsis under such conditions.

(*b*) In cases following a previous local infection of the skin, as a furuncle, etc., the sepsis follows the forms customarily seen in clinical practice, and the clinical varieties vary from very mild to very severe forms of general infection.

The cases of acute osteomyelitis occurring in nurslings and infants that are rapidly fatal because of the intense toxemia belong in this group, as the infection is most probably introduced through some surface (skin or mucous membrane) injury, as indicated previously in the discussion. In one of Bass' cases, *Staphylococcus aureus* was recovered from the blood.

(*c*) In dental practice a general infection is almost invariably associated with some form of dento-alveolar abscess usually of the periapical variety. Acute and chronic forms of "septicemia" have been described (Marshall, Thibault and Raison and others). The chronic form corre-

sponds to one of the clinical entities, referred to usually under the general term of "focal infection" in this country, and is of no interest in relation to the subject under discussion.

The acute form of general infection is the one that is of interest in this article. According to Marshall, this form has been seen in dental practice in association with periapical abscess; and, as referred to previously, Marshall and others expressed the belief that all periapical abscesses are of hematogenous origin when there are no surface indications of the infection having been transmitted into the interior of the pulp chamber. When limited to the periapical space, these acute infections are commonly very mild, are without general manifestations and are forerunners of the chronic form of sepsis referred to in the previous paragraph.

In surgical practice the clinical course is different. Almost invariably the substance of the jaw bone proper becomes infected, and a severe form of osteomyelitis results which develops coincidently with the general infection. Forms are described in which a general infection occurs as a sudden, acute, overwhelming exacerbation of a previously existing focus of infection, usually a dormant periapical abscess, and without the intervention of any operative or other form of trauma. These forms are unusual. Much more commonly the general infection is associated with some operative manipulation indicated by some dental condition. The following two groups are met in clinical practice:

1. Following some operative manipulation—extraction of a tooth, treatment for a periapical abscess, etc.—it is uncommon to have post-operative fever of high magnitude with corresponding subjective and objective symptoms. Undoubtedly, excessive temperature of this kind must be referred to transient bacteremias with corresponding states of general infection of similar evanescence. Commonly the cases in this group go on to complete retrogression and recovery as regards the general and local condition.

2. There are, however, a number of cases of general infection that, originating as do the cases in the previous group, nevertheless, go on and show a steady progression, even to a fatality. The numbers of these latter cases are not correctly appreciated by the medical profession. I usually see one or two of such cases in hospital and private practice each year. General infections of this type, of dental origin and of operative mechanism, are apt to be of a high order of intensity and malignancy, to be complicated by intracranial complications, and to be rapidly fatal within a very few days.

*B.* General infection occurring as a late phenomenon in the course of osteomyelitis of the jaw follows some form of trauma, either that occurring during a dressing of the wound, or that following operative

intervention. Clinically, general infection at any late stage of the disease, under the conditions specified, follows the form of development indicated in the immediately preceding two paragraphs (1 and 2) and with similar consequences.

Under any of these conditions, complicating nearby or distant lesions occur as a result of the transmission of the infecting bacteria through the blood stream. Some of these possible secondary conditions are also capable of being associated with a general infection. Commonly, one is faced with a combination of conditions, in which the general infection can be referable to either the original jaw infection, or its complication, as, for instance, a cavernous sinus thrombosis or a meningitis. Positive and negative blood cultures may be obtained in otherwise equally severe and fatal cases.<sup>2</sup>

In hematogenous cases and in those in which secondary general infections take place, metastatic foci can and do develop as a result of the bacteremia. Indeed, in some of the hematogenous cases the jaw lesion itself may be only one of many manifestations. These include (*a*) other bone lesions, (*b*) suppurative and nonsuppurative forms of arthritis, (*c*) infections of the various body cavities, (*d*) forms of endocarditis and pericarditis, (*e*) lung abscesses, (*f*) renal infarcts and (*g*) minor abscesses in the various fascial planes. These are common to all forms of hematogenous infections, and further discussion of them is beyond the scope of this paper.

*Local Complications.*—A group of complications occurs, which take place because of local extension of the disease. These complications include:

(*a*) The various abscess formations, including orbital abscess and empyema of the antrum, have been discussed previously. Rather uncommon complications that result from the pointing and rupture of the cervical forms of abscess include those described in the literature in which rupture took place into the larynx or trachea, or those that extended into the thorax.

(*b*) Ankylosis of the temporomaxillary articulation occurs as a result of involvement of the glenoid process in the lesion, or as a result of calcification of the muscular and tendinous tissues about the joint and upper part of the ascending ramus. This includes various forms of arthritis of the temporomaxillary articulation.

(*c*) Lesions about the angle and body of the lower jaw can rarely cause a phlebitis of the facial vein radicals, which, when once estab-

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2. The significance of positive and negative blood cultures in clinical practice in cases of acute infection has been discussed on another occasion (Wilensky, A. O.: Treatment of Infection: General Principles Underlying Treatment from a Surgical Standpoint and Therapeutic Indications to be Drawn Therefrom, Arch. Surg. 15:737 [Nov.] 1927).

lished, has a predilection for spreading upward into the cavernous sinus. I have the records of one private case, have seen one case in hospital practice and have seen one report in the literature. The last is reported by Coppens:

A man, aged 21, a wood-worker, except for a fracture of the arm and an attack of typhoid fever many years before, had never been ill. Fifteen days before admission he became suddenly ill with excruciating pain in the left lower jaw, with high fever, delirium and other signs of a general infection. Incisions were made in the gingivo-labial fold which gave little relief and showed a process in the lower jaw, but the illness was progressive thereafter until the patient died.

Postmortem examination showed an entire denudation of the entire left side of the lower jaw. The bone was necrotic and gangrenous; the process seemed to stop anteriorly at the median line, and to extend up to the temporomaxillary articulation. All the veins that have their point of origin in the inferior maxilla were full of pus; the external jugular vein was also full of pus, and the pus was traced up into the left cavernous sinus. The right side was healthy. A meningitis was also present.

(d) A very rare complication is meningitis. Coppens' patient also had meningitis.

(e) Sinus disease (empyema of the antrum of Highmore, usually with, and sometimes without, involvement of the major portion of the frontal, ethmoidal and sphenoid sinuses) complicates osteomyelitis of the upper jaw. Encephalitis appears as a secondary complication. Halloran's case was an example of this:

As indicated in another part of this communication, Halloran's patient had osteomyelitis of the upper jaw with an empyema of the maxillary sinus and roentgen evidence of pansinusitis. After drainage, the patient left the hospital in a much improved condition, only to return five weeks later with a progressive development of bilateral labyrinthine symptoms. At the peak of development, there were bilateral paralysis of the eighth nerve and paralysis of the left seventh and twelfth nerves. Laboratory tests gave essentially negative results. Improvement occurred in the manifestations referable to the seventh nerve; the paralyzes of the eighth were still persistent at the time of Halloran's report.

(f) Marchand mentioned cases of cerebral abscess that were reported as complications of osteomyelitis of the jaws. Under these conditions, cerebral abscess represents a further development of an encephalitis.

(g) In common with other wounds, wounds resulting from osteomyelitis of the jaws may be complicated by erysipelas and by tetanus.

#### TREATMENT

The general principles governing the treatment for acute osteomyelitis in general have been described on several previous occasions and will not be repeated here. For the present purpose suffice it to say

that cases of osteomyelitis of the jaws can be divided into the following groups:

Cases with clinical signs of a general infection.

Cases with few or no signs of a general infection, but with various grades of the local lesion.

Cases with complications.

As in previous parts of this communication, the odontogenous factors relating to the subject will be incorporated in the discussion as the occasion arises.

*Cases with Clinical Signs of a General Infection.*—1. Highly fulminant forms of general infection are usually of such a high order of severity as to render useless any form of local or general treatment. The group includes: (a) highly toxic cases occurring in nurslings and infants, (b) hematogenous cases following local surface (skin, mucous membrane, etc.) forms of infection in which the jaw lesion may be only one of several metastatic foci and (c) certain of the military injuries. Cultivations of the peripheral blood are practically always positive in the cases in this group. The prognosis is uniformly bad, and fatalities are to be expected.

2. In very sick patients with high fever and other clinical signs of general infection, cultivations of the peripheral blood are usually negative. Retrogression of the infection is common in the cases in this group spontaneously and occasionally as a recognizable partial or complete result of the form of treatment employed. However, a fatal outcome may occur subsequently either because of an intensification of the infection and a change from a sterile condition of the blood to one of bacteremia, or because of the occurrence of local or distant complications. The cases in this group include: (a) some of the severer cases of osteomyelitis following trauma and fracture of the jaw; (b) some military injuries and (c) cases of acute infection of the jaw following operative manipulation. In the latter cases, treatment should be persistently directed to the local condition, as detailed subsequently in this communication.

*Cases with Few or no Signs of a General Infection, But with Various Grades of the Local Lesion.*—The cases in this group consist of the bulk of the patients seen in practice, in which the problem is that of the local lesion and its local complications, principally abscess formation, and in which the question of general infection does not enter. In these cases the treatment resolves itself down to the best ways and means that will lead to the minimum loss of tissue, to the most rapid shedding of the sequestrums, to the most rapid healing of the wounds, to the greatest conservation of form and function and to the best general advantage to the patient.

Common accumulated experience and the literature make it evident that for the local lesion the general practice of conservation is the accepted principle of treatment at the present time. This is in accord with the theoretical considerations of the subject that I have made on several different occasions, and with which I am in complete accord. In lesions of the upper jaw, conservatism has been forced on the surgeon because of local anatomic and technical considerations; in lesions of the lower jaw, this has come about because of experience.

Ordinarily, the treatment for the local lesion itself should be considered under the following headings: (1) prophylaxis, including the treatment for any antecedent condition, (2) treatment for the local condition in the early stages and (3) treatment in the later stages.

(1) Effective treatment for any antecedent condition is necessary when the osteomyelitis follows some form of trauma and when it is associated with an odontogenous condition. It is beyond the scope of this communication to consider the traumatic conditions of the jaw (fractures, gunshot wounds, operative procedures, etc.) that are complicated by osteomyelitis.

The odontogenous conditions are, however, important, and adequate attention to them includes certain prophylactic measures.

Prophylaxis is the most important single item in the prevention of any local infection of the jaw bones from odontogenous sources. Generally speaking, the best one can do in regard to any form of general infection is also purely of a preventive nature. Most of the cases seen in practice are in association with odontogenous factors and occur as a result of unwise dental procedures or as unexpected consequences of apparently necessary manipulations even in very capable hands. The most important means at hand lie in the field of dental prophylaxis, which would tend to avoid, to decrease in numbers or to wipe out completely any form of dental infection. The importance of this simple means cannot be overemphasized, and fortunately this means of prevention of disease is being recognized more and more throughout the country. The next most important means of prevention of local or general infection lies in closer attention to the rules of asepsis in dental practice among the rank and file of the dental profession, and to appreciation of the great importance of gentleness in all dental procedures. For practical purposes, this comprises all that one can do especially in cases of general infection, because when once the infection has occurred, cure and healing depend on the relationship of individual resistance and the virulence and intensity of the infecting organisms; over this interaction of natural forces medical knowledge has little control at present.

Cases are well known, especially to the dental profession, in which apparently spontaneous exacerbations of infection extending into the



tissues of the jaw bones occur in previously existing periapical forms of dento-alveolar abscess. Efficient prophylaxis would prevent these accidents also, except in those cases in which the periapical abscess is itself manifestly a manifestation of a hematogenous infection.

In actual practice, infection of the jaws occurs as a complication of the following dental procedures:

(a) The extraction of teeth. It is a common practice among the dental profession to pack the teeth sockets after extractions. This one item accounts, in my opinion, for a very large proportion, if not the vast majority, of infections of the jaw, as the corking up of the secretions in the cavity of the tooth socket practically forces the infection into the bone tissue of the jaw. The dental profession should avoid this step, and should accept the policy of nonpacking after extractions as a prophylactic measure.

(b) The treatment for dento-alveolar abscesses of purely odontogenous extent and limitation. This, also, is a prolific cause for infection of the jaw bones. Many times infection of the jaw occurs because of the mere presence and the nature of the infecting organism and the lack of general and, especially, local resistance of the patient and the tissues. But here, again, infection is equally often aided materially by the lack of aseptic technic and by the lack of gentleness in the manipulations. For periapical abscesses, extraction of the tooth is the simplest and most common treatment; naturally, the prophylactic considerations detailed in the previous paragraph are applicable with increased force when infection is present.

The majority of periapically infected teeth do not require anything further than clean extraction. Curettement through the socket of the extracted tooth appears to me not only questionable but totally unadvisable. The apical contents, by such a procedure, are usually thoroughly macerated with the normal blood clot and remain in the socket, thereby creating an excellent culture tube. The bone curet in the hands of an unskilled operator is a dangerous instrument, especially so when that operator feels called on to curet all sockets after extraction, whether the case is an acute alveolar abscess or not. Many cases of osteomyelitis are the result of this form of treatment.

(2) Once an acute osteomyelitis has established itself in the bony tissues, it is important to recognize that in the early stages a period of extraordinary virulence of infection is present, usually lasting a very few days, during which any active or radical measures are likely to be productive of much harm, especially in the spread of the local infection and, possibly, even, as pointed out previously, in the production of a general infection. The importance of absolute conservatism throughout this stage is paramount.

In the presence of odontogenous conditions, no extraction should be made at this stage, nor should any other dental procedure be carried out. In the presence of any other preceding trauma or operation, due regard should be had to the dangers of causing an increased exacerbation of the infection and the possible creation of a general infection by the trauma incident to any dressing of the wound; certainly, under such conditions no further operative procedure should be undertaken, and any absolutely necessary dressings of the wound should be carried out most gently and with knowledge of the danger well in mind. During this stage of increased virulence, only the simplest measures necessary to proper cleanliness of the mouth should be practiced, and the contraindication to extraction or further manipulation should be absolute.

Benevolent change from the period of increased virulence is manifested by a lessening of the swelling of the tissues of and about the jaws, and by a perceptible decrease in the general and other local manifestations of bacterial infection. Any necessary dental condition that needs correction should be taken care of at this time, and in actual practice the procedure should be strictly limited to the extraction of definitely diseased teeth from which the local lesion apparently originated. The value and importance of the extraction lie in the fact that removal of the diseased tooth allows free drainage from any associated form of dento-alveolar abscess, and, by not doing anything else and, especially, by leaving the socket free from packing, it can be confidently expected that the odontogenous lesion will quickly and progressively retrogress thereafter. In cases of other etiology—especially operative cases—the policy of conservative passivity should be persevered in during this stage also.

In hematogenous infection of the jaws, the policy of conservatism during the early stages of development of the jaw lesion seems to me to be also of extreme importance. In these cases, the general principles underlying the treatment for acute osteomyelitis in general hold good, and, as so often happens in osteomyelitis of the irregular bones, this attitude is fortified and made imperative by anatomic and local technical considerations.

Sooner or later, in any of the varieties of acute osteomyelitis of the jaws, suppuration occurs; in most of the cases, the paths and localizations of these accumulations have been detailed in a previous part of this communication. From the point of view of efficient incision and drainage of these abscesses, the following classification is possible (see section on "Suppuration with Osteomyelitis of the Jaw," p. 206):

(a) In abscesses tending to point in the mouth, every effort should be made to drain as many of the abscesses as possible through the mouth. Many of the smaller abscesses, especially those of the gum-boil type, and those occurring in nurslings and infants spontaneously point and

rupture in the oral cavity, and no further attention is necessary besides efficient cleanliness. Other types of abscesses need incisions, which follow the usual surgical practice; abscesses of the cheeks can be reached in the angle between the cheek and the gum. Included in this group are all of the ordinary abscesses that form in association with the upper jaw on its palatal, alveolar and external aspects. As Marx pointed out, even some of the orbital abscesses and those forming on the face near the inner canthus of the eye can be reached from in front of the jaw by tunneling beneath the cheek from the reflection of the buccal membrane. In the lower jaw, the group includes all of the abscesses that gather above the line of attachment of the mylohyoid muscle and in front, and to the mesial side, of the pterygoid muscles; appropriately placed incisions in the floor of the mouth or at the buccal reflections will adequately care for these accumulations of pus.

(*b*) Abscesses that gather behind the upper jaw, or in relation to the condylar processes of the lower jaw, accumulate in inaccessible situations where incision is difficult. Practically, it is safer and better for one to await their spontaneous pointing and rupture into the mouth behind the palatal processes, or in front of the anterior margin of the ascending ramus of the mandible high up, than to attempt any incision; the danger of these inaccessible abscesses spreading in the reverse direction, especially upward toward the base of the skull, is, while known, negligible in practice.

(*c*) Abscesses in relation to the lower jaw and arising from lesions below the line of attachment of the mylohyoid or pterygoid muscles proceed, as was pointed out previously in this communication, in the general direction of the submaxillary and anterior triangles of the neck when the lesion is anterior to the angle of the jaw. The general rules applicable to the proper incision and drainage of abscesses of the neck in these locations apply here and need no repetition. It is important not to open these abscesses too soon, and it is equally important not to open them too late, in order to prevent tracking of the pus for any considerable distance downward toward the thorax, or inward toward the larynx and trachea, as was described under exceptional circumstances by Marshall and others.

(*d*) Abscesses in relation to foci at the angle of the lower jaw characteristically accumulate below and behind the angle of the jaw and tend to point there. The best incision for this accumulation is an angular incision below and behind the angle of the jaw; frequently, perfect drainage is possible by a stab wound and a large rubber tube drain just below the angle, when the abscess is sufficiently soft and large.

(*e*) Orbital abscesses should be treated most conservatively, as it is the rule for them to rupture spontaneously and for no disturbance

of vision to result. When the accumulation of pus spreads upward into the superior parts of the orbital cavity, incision is necessary and should be made through or under the eyelid. Healing occurs uneventfully.

(f) Antral accumulations of pus invariably discharge through the natural duct. It is practically never necessary in nurslings and infants to open the antrum from without, as abundant drainage results through the duct and through the sockets of the molars as these are exfoliated. In rare cases in adults, removal of any offending teeth is necessary, and the antrum must be effectively drained. Usually this can be done through the socket of the appropriate teeth; occasionally a much wider opening is necessary, and the latter should be made in the outer wall of the antrum above the alveolar border.

In acute osteomyelitis in infants, the extensive pathology includes most of the items and conditions included in this communication. In spite of its extent, conservative measures are best: hot fomentations in the beginning; cleanliness of the mouth and the nares; careful watching for presenting abscesses and their immediate opening, so that as little as possible in the way of disfiguring scar or deformity results; the avoidance of external incisions by clever and efficient care of orbital and antral complications; the withdrawal and removal of sequestrums and, above all, careful nursing and abundant nourishment; all of these are important in the final outcome of those who do not succumb to the initial general infection.

Commonly any of these abscesses is associated with much induration in the tissues in and about the jaw, and the emptying of the abscess nevertheless leaves a good sized swelling, which slowly disappears spontaneously and more quickly when aided by poulticing. The important rule to remember, however, is that no attempt should be made at the time the abscess is opened to execute any procedure on the bone itself; usually any such attempt is followed by increased swelling and induration, if by nothing more dangerous.

(3) The late stages of acute osteomyelitis of the jaws are characterized as the period in which sequestration occurs. The causes for this and the physical and anatomic characteristics of the various forms of necrosis have been detailed in previous parts of this communication. Efficient separation of the necrotic portions of the bone usually occupies from thirty to ninety days, depending on the area of necrosis and other local conditions. During this period suppuration is apt to be profuse both through the external sinuses and through the sinuses in the oral cavity about the teeth. Retention of pus is common, and new closed-off pockets may, and do, commonly, form, which need additional incisions. It is important to remember that during these incisions the aim should be to restore or create proper drainage for the accumulations of pus,

and on no account should any interference be made with the bony structure. The reasons for these precautions include:

(a) One is unable to recognize and distinguish adequately between necrotic and healthy viable bone, except through the plane of separation between healthy and dead bone.

(b) Sequestration, especially in the cases of more moderate extent, does not occur, or occurs in such small or limited extent as to be negligible; when of such small or limited extent, nature will take care of and properly exfoliate such sequestrums very much better and with less damage than can be done by the surgeon. In many of these cases, the pathology is that of a subperiosteal abscess pure and simple.

(c) When appreciable areas of bone necrosis occur, they are of minimal size commensurate with the position of the thrombophlebitic lesion and of its consequent disturbance of blood supply, when the natural process of sequestration is allowed to go on undisturbed.

(d) If interference with the bone structure is practiced at too early a stage, it most commonly results in an increase of the lesion and of the area of necrosis.

(e) In the lower jaw, the importance of waiting is paramount for the purpose of allowing sufficient involucrum to form so that the form and configuration of the lower jaw and the chin are retained. In the upper jaw, this consideration does not exist, as involucrum does not form.

These, too, are the considerations and reasons that decide the advisability of delaying the sequestrotomy until conditions are most favorable, so that no untoward consequences follow and so that the greatest conservation of form and function may be preserved.

Under such restrictions and conditions, the process of sequestration and its unaided or operatively aided exfoliation is reduced to its simplest form. Many times the sequestrum will be spontaneously discharged, or, during one of the dressings, a sequestrum presenting in the mouth of one of the sinuses can be easily withdrawn almost without the patient's knowledge; healing then proceeds quickly and efficiently. Both of these methods of termination are common for acute osteomyelitis of the jaw.

When some operative procedure is necessary for the removal of the sequestrum, the following simple rules should be remembered:

1. Whenever possible, and to as large an extent as possible, the operation should be done through the oral cavity.

2. Enlargement of any preexisting wound should be practiced only commensurate with the size of the sequestrum.

3. Chiseling away of any involucrum for this purpose should be done to the minimum degree, and should be so planned that the minimal

amount of deformity results. As a rule, very little of this is necessary. As was indicated previously, this applies practically exclusively to the lower jaw.

4. Any manipulation through the oral cavity or from the outside should be carried out in such fashion that a minimum amount of trauma is done to the muscular and tendinous tissues about the condylar and glenoid processes of the mandible, in order to prevent any calcification of these tissues and a consequent ankylosis of the temporomaxillary articulation.

5. Any external incision should be planned with due regard to a minimum of resulting visible scar.

6. Any necessary drainage should be instituted as far as possible from the inside of the mouth, and in the largest number of cases this can be done exclusively so. Then one can neglect any open sinuses that present externally, and it usually follows that the external openings promptly close.

Healing after secondary operations is usually a protracted affair, and the average case extends over a period of three or four months before complete closure is secured. Occasionally revisions are necessary, and during these procedures much the same rules should be followed. The important rule to remember is that the less one is forced to do, the less damage one is apt to do, the better for the local condition, and the quicker will be the subsequent healing.

Fry called attention to the frequency with which pathologic fractures occur in osteomyelitis of the mandible. This has not been so in my own experience. The diagnosis is made on the basis of deviation of the mandible from the midline to the affected side, crepitus and roentgen findings. The amount of displacement depends on the line of fracture, the presence of teeth on the smaller fragment with occluding teeth on the maxilla, and the amount of loss of bone. The general principles underlying the treatment are correct alinement, reduction of sepsis and immobilization of the fragments.

Dental splints should be fitted as early as possible to immobilize the fragments and thereby relieve the pain, reduce the danger of sepsis and allow the patient to take food more easily. Early surgical intervention by wiring or plating is contraindicated. Reduction of sepsis may be accomplished by constant irrigation, efficient drainage and the removal of septic teeth and teeth in the line of fracture. Splinting is used to aid the reduction of the displacement and to immobilize the parts. Immobilization is obtained by means of bandages and external supports, interdental wiring (of which there are four varieties) or dental splints.

In cases of osteomyelitis of the upper jaw even extensive necrosis does not necessarily mean extensive deformity, and one is constantly

surprised at the little change that is perceptible in the contour of the cheek and face. When the antrum has been exposed, healing is accompanied by epithelization of the cavity; the opening usually contracts but little, and commonly remains permanently. It is necessary to have an obturating appliance made to close the opening, and use can be made of the obturator to carry artificial teeth to replace those missing. Symptoms referable to the orbit disappear with the subsidence of the process and the healing of the lesion. Nasal symptoms usually need local attention for a little time, especially when, as so often happens, they are associated with disturbance in the antrum.

In cases of osteomyelitis of the lower jaw the involucrem results in an appreciable thickening of the jaw; the amount of deformity is, however, small. Dental appliances are necessary to make good the teeth that have been destroyed by the disease or as a consequence of operative manipulation.

When large portions of the jaw are lost, the remaining fragments are drawn toward each other by the contraction of the muscles, and the teeth are thrown out of occlusion, producing in many cases a great deformity, especially when the chin is swung to one side. To prevent this, it is necessary to keep the remaining portions of the jaw immobile and in proper alinement by fixation of the teeth in their normal occlusion. The simplest method is interdental ligation. Sometimes, because of a lack of teeth, a splint may be necessary, or even a vulcanite bar may be placed in the wound to maintain contour until new bone has formed; this bar can be removed and cleaned, and also can gradually be reduced in size as new bone is formed.

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# A REVIEW OF UROLOGIC SURGERY

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## KIDNEY

*Anomalies.*—Tachot<sup>1</sup> reported 12 cases of congenital malformation of the kidney. At nephrectomy the right kidney, which had been excreting purulent urine, was mistaken for the vena cava. The kidney resembled a long, cylindric sausage and ran from the bony pelvis to the normal renal region, at the right side of the aorta, just where the vena cava should be. An exploratory puncture elicited a brownish-red liquid, partly colloidal silver and partly blood, indicating that the organ was a kidney. Above the bladder the caliber of the sausage-shaped structure suddenly diminished and became a ureter slightly larger than normal and 5 cm. long. There was no true pedicle, and the vascular connections were so numerous and the denudation of this long tube so difficult that its extirpation required three hours. Embryologically it is explained that when the definitive kidney was formed, the nephrogenous mass presented adhesions with the twenty-third, twenty-fourth and twenty-fifth somites, preventing it from mounting in its entirety as the ureter progressed upward. The latter, crowned with a particularly plastic mass of renal tissue and meeting no obstacle to its ascent but the adhesions, arose to its normal place, carrying with it as much of the kidney as was free to rise, pulling it upward in this remarkable formation.

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1. Tachot: Pathology of the Kidney Affected with Congenital Malformation, Arch. d. mal. d. org. gén.-urin. 6:253, 1931.

The frequency of renal malformation suggests that, before proceeding to any operation on the "reno-ureteral" system; it should be determined whether there are two kidneys and whether they are in normal position. Neither the presence of two ureteral orifices at the two angles of the trigone nor the division of the urine with different concentrations of urea and different color is an infallible indication of the presence of two kidneys. In the diagnosis of renal disease the possibility of malformation must be considered, and significance attached to the presence of concomitant anomalies of the genitalia, which should always be thoroughly examined. The only true proof of the presence of the condition is obtained by roentgenographic and pyelographic examinations.

Donohue,<sup>2</sup> stated that the relief of obstruction of the upper part of the urinary tract with conservation of both kidneys is rarely accomplished in cases of horseshoe kidney. In the majority of reported cases, one kidney is generally found injured to such an extent as to require resection. In a recent case reported by Donohue, hydronephrotic changes were moderately advanced in one kidney as the result of obstruction at the ureteropelvic juncture. The obstruction was relieved by division of the isthmus connecting the two kidneys. Postoperative examination in this case has shown that the affected kidney has returned to normal.

Hess<sup>3</sup> reported a case of adenocarcinoma in a horseshoe kidney; the patient was a man aged 56. Resection on the right side was done. The vessels of the renal pedicle were abnormal in number, and were ligated and cut individually. A large piece of muscle was transplanted over the surface of the stump at the lower pole of the remaining kidney. The patient recovered from the operation. On examination a growth about 8 cm. in diameter was found. The diagnosis was adenocarcinoma.

[COMPILERS' NOTE.—A comparatively large number of tumors in anomalous kidneys, particularly of the horseshoe type, has recently been reported. Several cases of squamous cell tumor associated with stone have been found at operation. Apparently deficient drainage of the renal pelvis and an abnormal location, subjecting it to trauma, make the kidney more susceptible to infection, formation of stone and tumor.]

Jacobs<sup>4</sup> reported a case of ectopic pelvic kidney which was treated by nephrectomy. An unmarried woman, aged 25, complained of dysmenorrhea and abdominal tumor. Exploratory laparotomy revealed an ectopic kidney. Because the presence and condition of a second kidney had not been determined, the abdomen was closed and cystoscopy was

2. Donohue, P. F.: Division of Horseshoe Kidney for Relief of Ureteropelvic Junction Obstruction, *J. Urol.* **27**:59 (Jan.) 1932.

3. Hess, Elmer: Adeno-Carcinoma Horseshoe Kidney, *J. Urol.* **27**:47 (Jan.) 1932.

4. Jacobs, Arthur: Renal Ectopy, *Brit. J. Urol.* **3**:432 (Dec.) 1931.

done, which revealed a normal right kidney and a left pelvic kidney. Although no other abnormality was present, the kidney was removed to obviate hazard in a possible future pregnancy and to relieve the dysmenorrhea.

The incidence of renal ectopy is about 1 in 660 persons. It must not be confused with nephroptosis, which, although the predisposing factors may be congenital, is acquired. Renal ectopy is an embryonic developmental defect associated with vascular anomalies which check the upward migration of the kidney from the bony pelvis where it is situated in its earliest stages of development. It also fails to rotate, so that urography reveals the characteristic short ureter and the pelvis directed anteriorly instead of laterally. These observations, together with the anomalous vessels found at operation, which fix the kidney in an unusual position, distinguish the condition from nephroptosis. Its recognition is important because it simulates other abdominal conditions, and if the patients are women the abnormally situated organ may seriously complicate pregnancy and parturition.

[COMPILERS' NOTE.—Jacobs' case obviously is one of simple ectopia, that is, an embryogenic anomaly associated with the kidney lying at a lower level than normal, a blood supply arising from the aorta at a lower level than normal and a short ureter. At times the vascular pedicle may even arise from the iliac arteries and not infrequently from the aorta below its bifurcation. Because of the fixation of the kidney and its inadaptability to suspension, the preoperative diagnosis of ectopia in contradistinction to nephroptosis should be emphasized. A consideration of possible ectopic kidney is necessary in distinguishing tumors in the lower part of the abdomen from those in the pelvis. Interference with gestation is a frequent concomitant of iliac or pelvic ectopia. Under such conditions nephrectomy may be indicated. Ectopic kidneys are frequently poorly developed, often malformed and the seat of infectious or calculous disease.]

*Tumors.*—Alessandri<sup>5</sup> stressed the importance of the various means of roentgen diagnosis of tumors of the kidney. Simple roentgenography often shows the renal contour if the colon has been well emptied. Pyelography and urography with iopax are also useful. The injection of oxygen into the perirenal fat and pneumoperitoneum has been practiced by the author for several years. Four cases, 1 of renal carcinoma, 2 of hypernephroma and 1 of tubular carcinoma of the kidney, in which the latter methods made diagnosis possible, are reported in detail.

Because of the danger of producing emboli through rough handling of hypernephromas at operation, Alessandri devised a special incision

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5. Alessandri, R.: Accorrigimenti clinici e operativi per la diagnosi e la cura dei tumori del rene, *Ann. ital. di chir.* **10**:41, 1931; abstr., *Am. J. Cancer* **15**:3023 (Oct.) 1931.

which affords room to ligate and section the renal vein before freeing the tumor, even if it is large. The incision consists of a longitudinal limb, beginning at the costal margin just within the anterior axillary line and extending downward, and a transverse limb extending from the upper end of the longitudinal limb backward along the twelfth rib, which is resected.

[COMPILERS' NOTE.—So far as we know, injection of oxygen into the perirenal fat as an adjunct to roentgen diagnosis in urology is an innovation. Preliminary ligation of the renal vein as a one or two stage procedure in nephrectomy for tumor is, of course, a common practice in America. This is usually carried out through a transperitoneal incision or a Bazy modification of the Mayo lumbar incision. The incision described by Alessandri is novel in American practice.]

Jacobs and Hoffman<sup>6</sup> stated that a tumor invading the retroperitoneal perirenal fossa, when of the mixed cell sarcoma type, is highly malignant; myxomas, although only locally recurrent, are equally malignant. Treatment consists of complete extirpation of the kidney and tumor, including the adipose capsule. The perirenal fat should also be dissected from the peritoneum and from the muscles of the posterior abdominal wall. Radium and deep roentgen treatment at the site of nephrectomy should be applied immediately. The expectancy of life in these cases is less than one year. Recurrences at the original site are common and are immediately followed by generalized metastasis.

Crosbie and Pinkerton<sup>7</sup> reported the case of a woman, aged 35, with malignant leiomyoma of the kidney. The right kidney, which contained the tumor, was removed under spinal anesthesia, and convalescence was uneventful. The tumor occupied, roughly, the position of the pelvis and had greatly thinned the kidney over a large area at the upper pole. Microscopically, the tumor was found to be a leiomyoma originating in the outer wall of the pelvis. The authors stated that if this tumor had remained in the body, it might have become clinically malignant within a relatively short time. Propitious removal indicates that the prognosis will probably be favorable.

Dean and Pack<sup>8</sup> studied the cases of 16 patients with embryonal adenosarcomas of the kidney treated at the Memorial Hospital. Excluding the 1 adult in the series, the average age was 3 years. These tumors originate at different periods in the development of the embryo. One of the first symptoms of the disease is usually the accidental

6. Jacobs, L. C., and Hoffman, L. H.: Rare Renal Tumors, *J. Urol.* **27**:33 (Jan.) 1932.

7. Crosbie, A. H., and Pinkerton, H.: Malignant Leiomyoma of the Kidney, *J. Urol.* **27**:27 (Jan.) 1932.

8. Dean, A. L., Jr., and Pack, G. T.: Embryonal Adenosarcoma of the Kidney, *J. A. M. A.* **98**:10 (Jan. 2) 1932.

finding of a tumor in the abdomen, although pain, asthenia, malaise, hematuria or polyuria may be the initial evidence of the condition. When a large mass is palpable, the disease is widespread and the prognosis is unfavorable. The lesion generally extends by direct infiltration, but metastasis may occur through venous or lymphatic channels.

Surgical treatment of these tumors is unsatisfactory because of the tendency to recurrence. Although the growths are highly radiosensitive, irradiation alone has not effected cure; it does cause marked regression of the tumor and amelioration of symptoms in most cases, however. The authors are of the opinion that primary Wilms tumors should be treated by external irradiation. As soon as the growth has largely or wholly disappeared, nephrectomy should be performed. Metastasis or local recurrences are best treated by external irradiation.

Lieberthal<sup>9</sup> reported 7 cases of malignant tumors of the kidney of children. He stated that large abdominal tumors in infancy are usually malignant tumors of the kidney, the majority being mixed tumors of the embryonal adenosarcoma group. In lesions of this type sections should be taken from each part of the neoplasm in a search for the typical epithelial groups which will identify the tumor as an embryonal adenosarcoma. Inability to demonstrate these epithelial groups does not exclude the possibility that the tumor belongs in this group.

Embryonal adenosarcomas arise from the metanephros. The neoplastic change of the latter may occur at any stage in its development from the the mesodermal stage, where it is present only as metanephric anlage, to the point where actual metanephros has already differentiated. The earlier origin may be ascribed to cases in which striated muscle is present and the later origin to cases in which it is absent. The glomerulus-like structures in these tumors represent true embryonic glomeruli. The most significant symptom of malignant renal tumor of children is a rapidly growing, painless abdominal tumor. Hematuria is usually absent.

The general consensus among most surgeons is that treatment should be surgical, regardless of the size of the tumor, provided metastasis or severe cachexia is not present. Otherwise, death will occur within a year after the tumor is discovered. The youth of the patient is not a contraindication to operation. Israel reported a successful operation on an infant aged 3½ months, in which a tumor filling two thirds of the abdomen was removed. In a series of 20 patients not operated on observed by Albarran and Imbert, 14 died within six months, 3 within one year and 3 after one and a half years; only 1 survived three years. Death from recurrences and metastasis after operation

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9. Lieberthal, Frederick: Malignant Tumors of the Kidney in Childhood: A Report of Seven Cases of Embryonal Adenosarcoma, *Surg., Gynec. & Obst.* 53: 77 (July) 1931.

usually occurs within the first year, and it may occur as late as the fifth year. Israel advised a five year period of observation before considering a patient cured. Albarran and Imbert found the operative mortality to be about 25 per cent, although the total early and late mortality, including deaths due to recurrences and metastasis, reaches 86 per cent.

The median line incision was used in the cases reported by Lieberthal and is favored by most operators, as it enables better exploration of the abdomen for metastasis and aids in determining whether the tumor is bilateral. Israel favors the retroperitoneal approach, the line of incision following the long axis of the tumor. Voelcker's incision begins in the costovertebral angle and extends to the umbilicus; the peritoneum is opened widely.

[COMPILERS' NOTE.—Malignant tumors of the kidneys of children are rapidly fatal, and therefore the prognosis is poor. Most of the tumors appear during the first two years of life. They cause few symptoms. The pelvis of the kidney is generally not involved; consequently, hematuria and urinary obstruction are uncommon, and pain is rare. In the early stages the growths are small, firm, freely movable, localized to the region of the kidney and painless. When the tumor is moderately large, it often retains the contour of a normal kidney. The duration of symptoms is usually short before death occurs. Walker, in a series of cases in which operation had not been performed, found the average period of life after the onset of symptoms to be eight months; following nephrectomy the average period of life was sixteen months. In an occasional case the period of symptoms and growth of the tumors extends for several years.

The structure of the tumor is characteristic histologically. Many varieties of tissue have been described, but the predominating structures are groups of incompletely formed glands, surrounded by masses of irregularly disposed cells of an appearance somewhat similar to that of the cells forming the glands. They may contain striated muscle, squamous cell nests and more rarely areas of bone and cartilage. Magoun and McCarty stated that the growth is composed of one type of cell in various stages of differentiation and with varying amounts of connective tissue reaction. They classified the tumors as carcinoma of the adenomatous type. If metastasis or local extension has occurred, operation is often rapidly fatal. Death is certain if operative intervention is not carried out. Nephrectomy in most cases prolongs life and offers the patient the only chance of improvement. Earlier writers agree on the very high mortality.]

Rumpel<sup>10</sup> stated that the first objective changes in renal tumors consist of alterations in the contour of the kidney and its function.

10. Rumpel: Zur Diagnose die Nierentumoren, Zentralbl. f. Chir. 58:751, 1931; abstr., Am. J. Cancer 15:3023 (Oct.) 1931.



Subjective symptoms may be lacking or late in appearance. The function of the kidney, as measured by sodium indigotin disulphonate, U. S. P. (indigocarmine), is decreased following hematuria in cases of renal tumors. The function returns slowly to normal after the bleeding ceases. This phenomenon occurred in all the cases examined by Rumpel. Retrograde pyelography is preferred to the intravenous type in cases of tumor, and repeated examinations should be carried out in early cases to avoid error in diagnosis.

*Stones.*—Szenkier<sup>11</sup> stated that the diagnosis of nephrolithiasis is usually not difficult since a fairly definite syndrome is present. Infection of the appendix and gallbladder increases the difficulties of differential diagnosis when the calculus is on the right side. Blood cells in the urine, while suggestive of renal stone, have also been observed in cases of appendicitis. The Goldflam sign, or the elicitation of pain in the loin by a forceful blow, is not always pathognomonic, as it can also be elicited in other conditions such as a retrocecal appendix, pyelonephritis and renal tuberculosis. Occasionally the roentgenograms do not reveal the presence of renal stones.

Head's zones of hyperesthesia following renal attacks were mentioned. It has been observed only in cases of nephrolithiasis that, on grasping the abnormal side, the pain appears transmitted to the opposite side, similar to Guyon's renorenal reflex. Former explanations of the latter phenomenon compared it to sympathetic ophthalmia or the toxins of the diseased kidney affecting the normal side. By the work of Vernets and Mones it has been shown that there is an inferior mesenteric plexus in human beings. This solitary plexus is common to fibers from both kidneys. It is found in front of the aorta, at the juncture of the inferior mesenteric artery and aorta. To this plexus come the sympathetic nerve fibers of both kidneys, which call forth the following possibilities in cases of nephrolithiasis: (1) Pain stimuli originating in the diseased kidney go to the central plexus and give rise to pain in that kidney; (2) pain stimuli from the diseased kidney go through the plexus and into the segmental vertebral sympathetic fibers and then, stimulating the outer spinal segments, cause areas of hyperesthesia of the skin on the diseased side (Head's areas); (3) pain stimuli from the diseased kidney go through the plexus and call forth pain sensations in the normal kidney on the opposite side (renorenal reflex), and (4) there may be elicited both renal pain and areas of hyperesthesia on the sound side. It is Szenkier's belief that, although this sign of elicited pain referred to the sound side is not infallible, it can be of much aid in diagnosing nephrolithiasis.

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11. Szenkier, D.: Ein neues Symptom der Nephrolithiasis, *Ztschr. f. Urol.* 25: 250, 1931.

Weber<sup>12</sup> stated that three factors are significant in explaining the formation of urinary calculi: the mode of living, infection and urinary stasis. There may also be other unknown factors involved, particularly in cases of lithiasis occurring coincidentally with disease of the bone. Stone not uncommonly occurs in cases of disease of the bone complicated by infection, such as comminuted fractures, chronic vertebral ankylosis and infectious arthritis.

The following cases were mentioned: bilateral calculus associated with an amputation of both thighs; passage of sixteen stones following ankylosis of the hip of long duration, together with much infection; left renal calculus developing after fracture of the femur complicated by infection and the formation of a sequestrum. There were several cases of coxitis, as well as a case of involvement of the bladder following injury, in which urinary calculus resulted. In a case of simple tibial fracture the bone did not unite in six months, and later calculi of the urinary tract developed.

Weber is of the belief that sudden inactivity as the result of a fracture lowers the usual carbon dioxide exchange and affords an opportunity for it to combine with the calcium salts, resulting in the formation of stone.

[COMPILERS' NOTE.—Weber's observations on the incidence of urinary lithiasis and disease of the bones are noteworthy. From time to time reference to such association has been made, but it has been difficult to establish any causal relationship. One would presume that infection might play an important part in spite of Weber's contention that a metabolic disturbance of the carbon dioxide exchange is at fault.]

Eisenstaedt<sup>13</sup> considered certain etiologic factors in the formation of urinary calculus. Urinary stasis, from whatever cause or wherever situated, is significant; infection of the urinary tract is subsequent to and dependent on this condition. If the infecting organism is a urea splitter, the likelihood of formation of stone is markedly increased.

In a series of fifty-five stones examined, the nuclei contained bacteria, which appear to be material factors in their production. The hydrogen ion concentration of the urine is significant and seems to be a factor in the precipitation of urinary salts. In cases of lithiasis the hydrogen ion concentration of the urine obtained from the diseased side is usually higher than that from the healthy side. Recent experimental work indicates that the so-called protective urinary colloids may not be as important as supposed. Deficiency of vitamin A seems to be an indirect

12. Weber, W.: Steinbildung und Knochenerkrankungen, *Ztschr. f. Urol.* **25**: 36, 1931.

13. Eisenstaedt, J. S.: Certain Tangible Factors in the Etiology of Urinary Calculus, *Surg., Gynec. & Obst.* **53**:730 (Dec.) 1931.

contributing factor in the experimental formation of calculi, producing increased susceptibility to infection in general and particularly in the urinary tract.

[COMPILERS' NOTE.—Eisenstaedt's comment that urinary stasis is a significant factor in formation of stone is generally accepted by other observers. Stagnation invites the stone-forming process and enhances the chance for deposition of stone-building material. The significance of bacteria in the nuclei of stones is not so clear, nor can we agree that the part played by hydrogen ion concentration has been properly established as a causal factor. Furthermore, what we do know of the mechanism of formation of calculus is definitely linked with the colloidal solvent mechanism of the urine or its imbalance. The mechanism whereby deficiency of vitamin A produces stone is yet to be determined. Not yet can it be stated definitely that this type of formation is or is not associated with infection. This could well be the next point of attack on the problem.]

*Hydronephrosis.*—Walters<sup>14</sup> stated that most cases of hydronephrosis are the result of definite obstruction at the ureteropelvic juncture. The causes of such obstructions are usually anomalous renal blood vessels, peripelvic connective tissue causing angulation or collapse of the ureter, narrowing of the ureter at the ureteropelvic juncture due to subepithelial fibrosis and obstruction of the ureteropelvic juncture due to lateral insertion of the ureter. The indications for conservative surgical procedures for hydronephrosis are limited to cases in which the hydronephrosis involves both kidneys, or in which it involves one kidney of which sufficient parenchyma remains to justify preservation of the organ.

Fourteen cases in which removal of the obstruction had been combined in some instances with nephrostomy and nephropexy were considered. Whether division of anomalous blood vessels obstructing the ureteropelvic juncture can be performed without too much disturbance of the blood supply to the kidney should be determined before they are severed by temporarily occluding them by means of a rubber-covered hemostat. After division of the anomalous vessels, the ureteropelvic juncture must be at the dependent portion of the pelvis, and the pelvis must be drained efficiently or symptoms of obstruction will continue. Resection of the renal pelvis has been performed in cases in which the pelvis was greatly dilated, and the laterally inserted ureteral orifice was collapsed with the distention of the renal pelvis. In these cases resection was carried out so that when the pelvis was closed, the ureteral orifice became dependent, adequately draining the kidney.

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14. Walters, Waltman: Evaluation of Results of Conservative Surgical Treatment of Hydronephrosis, Proc. Staff Meet., Mayo Clin. 6:712 (Dec. 2) 1931.

Postoperative complications that may occur are obstruction at the ureteropelvic juncture, with retention of urine in the renal pelvis; infection of the renal parenchyma, with formation of cortical abscess, and extravasation of urine about the kidney. The various operative procedures carried out by Walters have given satisfactory results as measured by the following effects: disappearance of symptoms of obstruction of the urinary tract, such as pain and fever; return of the size of the renal pelvis and calices to within normal limits; absence of retention of urine in the kidney, and improvement in renal function subsequent to operation.

[COMPILERS' NOTE.—The conservative surgical attack on the pelves of hydronephrotic kidneys is one of the developments of recent years. The contributions of Quinby, Walters and others to this work are stimulating and promising. Recently Young described a procedure whereby the renal pelvis is resected in this manner and its remainder so sutured that it is drawn away from the constricting anomalous vessel without the latter being sacrificed. The emphasis placed by Walters on the establishment and maintenance of drainage of the renal pelvis at its most dependent position at the conclusion of the operation is noteworthy. This seems to be the important point in the procedure.]

*Tuberculosis.*—Caulk<sup>15</sup> stated that renal tuberculosis is less common because of early diagnosis and improved treatment of pulmonary and general tuberculosis and the prevention of massive lesions. Early diagnosis in renal tuberculosis is paramount.

In unilateral renal tuberculosis, nephrectomy should be performed promptly. The immediate relief of symptoms in many of these cases after operation is due to the removal of a tuberculin reaction created by the products of bacteria, tuberculoproteins, fats and fatty acids. Often the more acute the lesion in the bladder, the more quickly the healing and relief of symptoms follow removal of the diseased kidney. The possibility of healing in chronic renal surgical tuberculosis is remote and not comparable to that of simple early experimental lesions. The mortality of nephrectomy for this condition is low, and relief of vesical symptoms may be expected in at least 75 per cent of cases of unilateral renal disease, whereas invalidism is almost inevitable if patients are left to medical care. A comparison of the results in patients with renal tuberculosis treated by nephrectomy and in those treated expectantly indicates the ineffectiveness of medical treatment. Parsons, in 1925, pointed out that 85 per cent of the patients treated medically were dead within five years. Wildbolz, in 316 cases in which no operation was performed, found that 58 per cent of patients died within five years and only 6 per cent lived more than ten years. Of 104 patients on whom he performed nephrectomy for renal tuberculosis, 55.7 per cent were

15. Caulk, J. R.: Renal Tuberculosis, *J. Urol.* 26:189 (Aug.) 1931.

completely well at the end of ten years. Sutter reported 61 per cent well between eleven and seventeen years after operation. In 863 cases at the Mayo Clinic, 58.1 per cent of patients were cured four years after operation. In Caulk's series of cases, 56 patients (51.9 per cent) have been traced. Forty-three (77 per cent) of these are well and free from vesical symptoms; 23 per cent still manifest evidence of the disease or have died.

In cases of bilateral renal tuberculosis, surgical procedures are indicated only in cases of emergency to relieve the patients of toxemia from pyonephrosis or to correct intractable vesical lesions.

[COMPILERS' NOTE.—Operation for early unilateral tuberculosis of the kidney receives a challenge from time to time. The contributions of Thomas on this subject in the last few years are noteworthy. Caulk, however, voiced the opinion held probably by most urologists, that under such conditions nephrectomy is the procedure that offers the greatest possibility of cure. Operation for certain reasons may be contraindicated, but those who advocate medical treatment should bear in mind that temporizing with unilateral renal tuberculosis may lead to such extension of the tuberculous process that the patient will ultimately be subjected to greater operative hazard in an attempt at cure.]

Hunt<sup>16</sup> stated that primary renal tuberculosis probably never occurs, as the kidney alone is seldom the site of tuberculosis. It is a rather common surgical lesion of the kidney, constituting 28 per cent of the lesions for which nephrectomy has been done in Hunt's experience.

Ten years ago it was generally accepted that nephrectomy was the preferred treatment in cases of unilateral renal tuberculosis. Even with evidence of associated tuberculosis elsewhere in the body in approximately 80 per cent of cases of renal tuberculosis, the patient should not be deprived of the benefit to be obtained by removal of the major tuberculous lesion, provided the latter is unilateral renal tuberculosis. Nephrectomy was justified in such cases because of the low primary mortality rate of about 2 per cent, even though there was moderate pulmonary involvement. Bilaterality of the disease was a distinct contraindication to nephrectomy, unless acute unilateral complications were present. In the presence of associated tuberculosis, nephrectomy was only a part of the treatment.

Medlar recently concluded that the kidneys of patients dying of pulmonary tuberculosis are commonly involved. In his experimental work with animals in which miliary tuberculosis was produced, it has been shown that renal tuberculosis is common in the guinea-pig and that bilateral involvement is the rule. Thomas, in 57 per cent of the cases in

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16. Hunt, V. C.: When Should a Tuberculous Kidney Be Removed? *West. J. Surg.* 40:40 (Jan.) 1932.

which renal tuberculosis existed, found bilaterality of the disease, and stated that since all renal infection in which bacilli of tuberculosis are present is hematogenous in origin, both kidneys are infected equally, and that bilateral infection is the rule.

Two years ago Hunt reviewed 838 cases of renal tuberculosis observed at the Mayo Clinic during the period from 1919 to 1929 to determine approximately the incidence of bilaterality of the disease. Nephrectomy was performed in 574 (68 per cent) of these cases. In the 264 cases in which operation was not done, nephrectomy was advised for but refused by 43 patients. The operability by nephrectomy was 73 per cent. In the remaining 221 cases, a definite diagnosis of bilateral involvement was made in 91. From the clinical evidence a diagnosis of bilateral renal involvement was made in only 111 (about 13 per cent) of the entire series. Wildbolz reported a mortality rate of 40 per cent within ten years, stating that more than half of the deaths were due either to tuberculosis of the remaining kidney or to tuberculosis elsewhere. Braasch had previously reported 20 per cent of deaths within five years after operation from similar causes. Assuming that half of these deaths may have been the result of tuberculosis of the remaining kidney, Hunt is of the opinion that a primary or late incidence of 25 per cent bilateral involvement is a liberal estimate in renal tuberculosis.

*Perinephritic Abscess.*—Fowler and Dorman<sup>17</sup> stated that perinephritic abscesses are usually classified as primary and secondary. In the primary group are included all cases in which the primary focus of infection lies outside the kidney. In the secondary group the primary lesion is in the kidney, the perirenal tissues becoming infected secondarily as a complication or sequel of the renal disease, either by direct extension from or rupture of the primary focus. This occurs particularly in cases of pyonephrosis, either calculous or tuberculous. From the standpoint of diagnosis the secondary group is not so significant. The primary renal lesion is the one requiring attention, and usually is readily recognized by urologic study; the treatment is directed primarily to the intrarenal lesion.

Fowler and Dorman considered the so-called primary or metastatic type of the disease. It is evident from a study of the reported cases that staphylococci are the infecting organisms in an overwhelming majority of cases of true perinephritic abscess. Multiple abscesses may form secondarily in various tissues and organs, such as bones, lungs, kidneys and muscles. In children the bones are most frequently infected by acute osteomyelitis; in adults infection of the kidneys is the most significant complication. It has been shown experimentally that trauma is instrumental in the development of perinephritic abscess. A history of injury is frequently obtained in these cases.

17. Fowler, H. A., and Dorman, H. N.: Perinephritic Abscess, *J. Urol.* **26**: 705 (Dec.) 1931.

There is no pathognomonic sign by which an early diagnosis can be made. Pain is generally a constant early symptom, coming on quite suddenly and without reference to the patient's activity. It may be severe or of a mild, dull aching type. It is definitely localized over the affected kidney and usually not referred. The majority of abscesses are situated posteriorly to the kidney, producing the maximal point of pain or tenderness in the costovertebral angle. Fever of the septic type is present in all cases, the temperature varying daily as much as 4 degrees. Signs of sepsis soon accompany these symptoms. The urinary findings are usually negative.

Diagnosis should be made as soon as possible in order that destruction of the kidney as well as other complications, sepsis and abscess of the lung may be avoided. Recent infections such as boils, carbuncles, paronychia, tonsillitis and infections of the skin should be carefully noted.

Free drainage should be established in every case as soon as a positive diagnosis is made. The usual oblique lumbar incision should be employed, with ample space to explore the kidney easily and thoroughly. After the main abscess is opened and drained, a careful exploration of the parts should be made with the finger to make sure that all pockets are freely opened and drained. Exploration of the entire kidney to rule out multiple abscesses will often hasten recovery and prevent subsequent operation. Cases of tuberculosis, pyonephrosis or multiple cortical abscesses may require nephrectomy. This is best performed later, after thorough drainage has been established with subsequent cleaning of the wound.

[COMPILERS' NOTE.—The danger of overlooking perinephritic abscess in cases of obscure sepsis is called to attention frequently. The insidious onset, the variable degree of pain and the absence of urinary symptoms often serve to deceive even an astute clinical observer. Emphasis is placed on care to determine the presence of pain in the costovertebral angle. The use of the exploratory aspirating needle is advocated by some, and if carried out with due care not to injure the pleura or viscera seems to have a place in diagnostic procedure. With the establishment of a probable diagnosis, surgical exploration and drainage as advocated by Fowler and Dorman is the operation of choice. Nephrectomy, if necessary, may be better carried out at a later date when the condition has become chronic. The main points in the diagnosis of perinephritic abscess are tenderness in the costovertebral angle, obliteration of the border of the psoas muscle, leukocytosis, intermittent fever and, at times, a history of previous infection of the urinary or extra-urinary tract. In late cases there may also be a slight curvature of the spine away from the infected side.]

## URETER

*Anomalies.*—Lepoutre, Laurent and Berthelot<sup>18</sup> stated that it was impossible to discover an extravasical outlet of the ureter in the male before urethrocystoscopy came into use, and the only reported cases were found at necropsy. In the male an outlet into the posterior urethra does not cause incontinence of urine, since the abnormal ureter never opens in front of the verumontanum. It is revealed only by an infectious complication, the abundance and intermittency of the pyuria serving as guides. If urine is replete with pus over a period of months or years, it can be explained only by pyelorenal suppuration. Examination of secretion expressed from the prostate gland determines how much infection comes from this gland. If the urine is perfectly clear from time to time, the pyuria must have its origin above. In the majority of cases anomaly of the ureter is accompanied by a double kidney and duplication of the ureter on the affected side. The presence of an abnormal orifice in the posterior urethra is brought into view by the urethrocystoscope, and a catheter passed into this will elicit a liquid similar to urine. This ureter, the terminal extremity of which passes through an inextensible organ, subject to congestive attacks, is greatly exposed to dilatation and infection, and the associated kidney has a precarious future. Frequently the abnormal portion of the urinary system is transformed into a vast ureteropyonephrosis. If the kidney is single, the treatment is like that for any other form of pyonephrosis. If the kidney is double, an effort should be made to remove only the diseased portion. If the lower part of the ureter is not removed and is infected, it will become the source of new disturbances. The lower part of the ureter should be resected to the point where it enters the prostate gland. Otherwise, it will require subsequent operation.

[COMPILERS' NOTE.—The problem of an ectopic ureter opening extravasically has been thoroughly considered in the literature from the embryologic and clinicopathologic points of view. Dossot of Necker Clinic tabulated from the literature 154 unusual cases, 46 of which occurred in males. Clinically, it has been demonstrated that since there is no sphincter action at the mouth of the ectopic ureteral orifice there is always ascending infection, causing dilatation of the whole upper part of the urinary tract. The association of other anomalies is also common, and the proper treatment, whenever this condition is determined by urographic methods, is the combined method of ureteronephrectomy, or, if a double kidney is present, ureteroheminephrectomy.]

18. Lepoutre, C.; Laurent, G., and Berthelot, J.: Outlet of the Ureter into the Prostatic Urethra, Arch. d. mal. d. org. gén.-urin. 6:310, 1931.



Gibson<sup>19</sup> reported a case of supernumerary ectopic ureter. The patient was a man, aged 20, who had persistent pyuria. Urography showed a left double kidney, the uppermost pelvis of which was dilated and communicated with the posterior urethra by means of an enormously dilated, tortuous ureter. The lower pelvis opened normally into the bladder. There was also an unusual anomaly of the fifth lumbar vertebra and the sacrum. The whole left side of the sacrum was oversized and the left innominate bone was considerably larger than the right. There was a tilt in the lower part of the dorsal spine apparently due to anomalous wedging of the dorsal vertebra.

Gibson concluded that the case emphasized the significance of congenital anomalies as an immediate or predisposing cause of pathologic conditions arising in the genito-urinary tract, and illustrated the frequent association of anomalies of the urinary tract with other anomalies. A thorough urologic investigation should be carried out in all cases of pyuria which do not respond to medical treatment. Treatment is usually heminephrectomy, including ureterectomy.

A series of 100 cases of ureteral ectopia was reviewed by Kilbane in 1926, and in 1928 Thom, of Bier's Clinic, reviewed 185 cases. In 1930 Sargent reported a case of ureteral ectopia and found that of 186 patients, 123 were females and 63 males, a ratio of approximately 2:1. It was noted that the condition of most female patients was diagnosed during life, whereas practically all male patients came to necropsy. This is due to the fact that ureteral ectopia of the females is accompanied by incontinence, since the ureters open either within the external urethra or vulva or within the vagina or uterus, causing constant urinary leakage in spite of normal urinary function.

*Tumors.*—Chauvin and Cerati<sup>20</sup> reviewed from the literature 112 cases of primary ureteral tumors, to which they added 4 of their own. Men were more often affected than women; the ages varied from 22 to 90 years, with the highest incidence at 60. The incidence of calculi varies from 21 per cent (Albarran) to an incidence of 5 in 35 cases reported by Kretschmer. Leukoplakia in the upper part of the urinary tract is relatively rare as compared with its occurrence in the oral cavity. It was associated with only 8 cases in this series. The distribution of the tumors anatomically is reported as being even with respect to the two sides. The most common site of the new growth is at the normal points of ureteral constriction, namely, the two extremities and the brim of the pelvis. The tumors in this series were usually single and

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19. Gibson, T. E.: Supernumerary Ectopic Ureter, *West. J. Surg.* **39**:280 (April) 1931.

20. Chauvin, E., and Cerati: Les tumeurs épithéliales primitives de l'urètre, *Arch. d. mal. d. org. gén.-urin.* **5**:631, 1931; abstr., *Am. J. Cancer* **15**:3028 (Oct.) 1931.

small. Metastasis was noted in only 5 cases, and in each instance different organs were involved. It is believed that the mechanical difficulties due to the presence of the tumor cause death in most cases before metastasis can develop. Local extension and implantation in the lower part of the ureter and trigone of the bladder occur more frequently. The benign papillary growth was noted in 36.6 per cent of the cases. Of the malignant neoplasms, papillary carcinoma was the most common; 20 were atypical, infiltrating growths and 8 were basal cell carcinomas.

Hematuria was the main symptom. The prognosis is grave, even in benign papilloma, on account of a serious renal complication.

*Stones.*—Dourmashkin<sup>21</sup> stated that there are many cases in which stones are passed that never come to the attention of a physician. Cystoscopic manipulation was carried out in practically all of his series of 565 cases.

Cystoscopy is indicated in all cases of acute renal retention in order to establish drainage and thereby prevent infection. It was possible to pass the obstruction in 114 of 137 cases of acute renal retention in Dourmashkin's series. The urine escapes through the catheter with great force, sometimes in a continuous stream. Although only a small percentage of cases shows evidence of severe renal infection as a result of obstruction by stone, the best method to combat the infection is through the establishment of drainage by means of an ordinary catheter. Unless the stone protrudes from the ureteral orifice the passage of catheters in acute cases is sufficient. Metallic dilators, rubber bag catheters or other massive instruments should not be used during an acute attack. The indwelling catheter is of great value in acute cases. Including the chronic cases, it was used in 237 cases in this series. Its usefulness is limited in chronic cases in which the calculus is usually large, because ordinary catheters do not produce sufficient dilatation to allow the stone to pass. In acute cases the catheters may be left indwelling from one hour to several days. In chronic cases the proper application of the modern technic of cystoscopy may result in the reduction of open operations, especially when the stone is situated in the lower end of the ureter. In these cases the calculus usually measures more than 0.5 cm. in width and there is a history of repeated attacks of renal colic. The stone in these cases is arrested on its way down because of impaction and relative narrowing of the ureter, and treatment should be directed toward the removal of these obstacles.

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21. Dourmashkin, R. L.: The Basis for Management of Ureteral Calculi: Based on the Study of Five Hundred and Sixty-Five Cases, *J. A. M. A.* **98**:276 (Jan. 23) 1932.

Ureteral meatotomy was performed in 104 cases. It may be considered a harmless procedure, although in 1 case an alarming hemorrhage ensued from its use.

At least a week should be allowed to elapse between treatments. If the dilation has been ample and little if any edema is present, the stone may pass from the ureter without colic; ordinarily the expulsion of the stone is preceded by an attack of renal pain.

In 1,467 cystoscopic manipulations, including the initial examination, there were no deaths. In 100 cases in the entire series, stones more than 0.6 cm. in diameter were passed without operation. The advantages of cystoscopic manipulations are mainly economical.

[COMPILERS' NOTE.—Dourmashkin reported a fairly large series of cases with no mortality, and, as he expressed it, the main advantages of this type of removal of ureteral stones are economical. On the other hand, not infrequently several attempts are necessary to remove the stone, in some cases associated with much discomfort. It must not be forgotten that the risk is also small following the open operation for removal of ureteral stone. In a report of 640 cases of ureteral stone removed by operation, published in 1925, there were only 4 (0.62 per cent) deaths. There were no deaths following uncomplicated ureterolithotomy. In the 4 cases in which death occurred, either other surgical procedures were also carried out, or other disease of the urinary tract was partly responsible for the death.]

*Obstruction.*—Young<sup>22</sup> stated that obstruction at or near the ureteropelvic juncture is not infrequently caused by vessels which pass from the great vessels to the lower pole of the kidney. Two cases are reported in which these vessels caused an acute flexure, kinking and obstruction of the ureter, bilateral in one case and unilateral in the other. In the bilateral case the less affected kidney was operated on first. The aberrant vessels obstructing the ureter were clamped, divided and ligated, after which there was a postoperative reduction in the function of the kidney on this side. Drainage of a huge hydro-nephrotic sac was continued for more than a month by means of a retained ureteral catheter passing out through the penile meatus. This resulted in restoration of the kidney to practically normal function, so that it was possible to save it and to carry out the conservative plastic operation on the pelvis with excellent results. At the second operation Young performed a new procedure by means of which it was possible to resect the redundant pelvic sac and, in closing it, to draw the ureter

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22. Young, H. H.: Obstructions to the Ureter Produced by Aberrant Blood Vessels, *Surg., Gynec. & Obst.* 54:26 (Jan.) 1932.

away from the veins so as completely to remove the possibility of obstruction. A satisfactory result was obtained in this case. The same procedure was done in the second case, with complete success.

*Transplantation.*—Coffey<sup>23</sup> reported on the origin and progress of his method of transplantation of the ureters into the large intestine. The principle on which his operation is based is that of the physiologic valve which permits the delivery of fluid from a duct in which the pressure is low into a hollow viscus in which the pressure is high. The valve, which must be distinguished from a sphincter, is produced by the duct running for some distance in the wall of the hollow viscus before it enters the lumen. The importance of this arrangement in preventing regurgitation of contents and dilatation of the duct was discovered during experiments on pancreatectomy in which transplantation of the common bile duct into the intestine was necessary.

Coffey's operation has been modified and improved so that three distinct procedures have been developed. The first procedure consists in drawing the ureter into the interlamellar space immediately beneath the intestinal mucosa, its split end being drawn through an opening made in the mucosa at the caudal end of an uncompleted intestinal incision and anchored inside the intestine; thus the open ureter is brought into the intestinal lumen at the time of operation. One ureter is transplanted at a time to allow for the subsidence of edema. It is the method most frequently used because of its priority and applicability to exstrophy of the bladder in children. In the second procedure a tube or catheter is fastened within the ureter by ligatures which both seal the ureter against intestinal infection and anchor it to the catheter; after this the catheter is passed through an opening made in the mucosa at the caudad end of an uncompleted intestinal incision, and is used to draw the ureter into the interlamellar space beneath the intestinal mucosa and through the opening in the mucosa into the intestinal lumen. The urine is transmitted from the upper part of the ureter through the catheter into a receptacle outside the body. The anastomosis is completed, and the open ureter exposed to intra-intestinal pressure only after the intra-intestinal end of the ureter sloughs and permits the catheter to come away, from eight to sixteen days after operation. The development of this technic has greatly increased the indication for ureterorectostomy because it is applicable when the ureters are dilated and when there is a single kidney, but mainly because it permits the simultaneous transplantation of both ureters at a single operation. It is the method of choice in carcinoma of the bladder, vesico-

23. Coffey, R. C.: Transplantation of the Ureters into the Large Intestine. Submucous Implantation Method, Personal Studies and Experiences, *Brit. J. Urol.* 3:353 (Dec.) 1931.

vaginal fistula and intractable bilateral renal tuberculosis. In carcinoma of the bladder in the male, total cystectomy may be combined with this operation with little additional risk. In the female this is not practical, and destructive doses of radium may be applied or the bladder may be removed at a second operation.

The third procedure is still in the experimental stage. Because of its simplicity it will probably supplant the first procedure in cases of exstrophy of the bladder. Only one ureter can be transplanted at a time. The ureter is brought into the interlamellar space outside the intestinal mucosa by an anchor stitch which fastens the end of the ureter in the angle of the caudal end of an uncompleted intestinal incision. The anastomosis is gradually made by a tightly tied suture which transfixes both the ureter and intestinal mucosa. The anastomosis is complete three or four days after operation.

It is apparent that with these operations there should be a high ultimate mortality because it is inherent in the conditions for which the operation is performed. In cases of carcinoma it will depend on the type of cases accepted for treatment. In the hands of a skilled abdominal surgeon the operative mortality should not exceed 5 per cent. Intravenous urography and analysis of the blood show in many cases progressive hydronephrosis and some renal insufficiency.

The operation is performed only in cases in which there is some intolerable condition. The results in 48 cases reported justified the risk.

[COMPILERS' NOTE.—Coffey reviewed the development of his technic of uretero-intestinal anastomosis, a procedure that if ultimately perfected will do much to change the course of urologic surgery. The average high mortality of the operation has mitigated against its popularity. However, the application of the method by its author, C. H. Mayo and others has been attended by results that show that the operation has passed the experimental stage and is at present adaptable to a considerable group of cases.]

The opportunity for total cystectomy and for resection of the prostate gland in cases of carcinoma could well be afforded by uretero-intestinal anastomosis. However, successful issues from such operative procedures are infrequently reported. We must as yet consider the Coffey operation in a stage of development, but what has been done with the method offers much of future promise.]

*(To be Concluded)*

# ARCHIVES OF SURGERY

VOLUME 25

AUGUST, 1932

NUMBER 2

## PULMONARY ABSCESS

JOHN L. YATES, M.D.

MILWAUKEE

Abscesses result from invasion of tissues by parasites of sufficient stamina to maintain destructive activities despite the resistance proffered by the host. Unimpaired lungs of robust persons are extremely resistant to invading bacteria; their defensive capacity is extraordinarily high, and they are able to effect relatively scarless repair of sizable lesions. The peculiarities of structure and function of the lung that provide these attributes likewise disclose the pathogenesis of pulmonary abscess and indicate appropriate therapeutic measures.

### STRUCTURE OF THE LUNGS

A unique disproportion in the enormous expanse of the five surfaces of the lung and its limited parenchyma richly supplied with blood are the significant structural characteristics. The external or ventilating surface is formed by the bronchial mucosa and the cells lining the 404,000,000 alveoli. The aerating surface is formed by the endothelium lining the capillaries of the lesser circuit, which is devoid of vasomotor control. The nutritive surface is formed by the capillary endothelium of the bronchial vessels provided with vasomotor control. The drainage surface is formed by the endothelium lining the lymph vessels. The pleural surface is formed by mesothelium lying on the subserosa.

The parenchyma, composed of connective tissue, muscle, elastic tissue and reticulo-endothelium, is distributed between surfaces and about air ducts, vessels and nerves. It provides support, yet augments the elastic recoil.

### FUNCTION OF THE LUNGS

The more significant functions are external respiration or aeration of blood, filtration of inspired air, filtration of blood delivered through pulmonary and bronchial arteries and elaboration of antibodies. External respiration is assured by the intimate approximation of alveolar and pulmonary capillary walls so long as air passages are unobstructed and blood is circulating normally. The total expanse of the walls of alveoli at the end of inspiration fluctuates in an adult from 79 sq. m. during rest to 129 sq. m. during maximum activity (Aeby), or from forty

to seventy-five times the average area of the skin. The total expanse of capillary walls, which are similarly elastic, is not materially smaller.

Aeration of blood, a basic function because all activities, including defense against disease and life itself, are commensurate with its integrity, depends on the preservation of the normal relationships between these surfaces. The volume of inspired air is a chief factor in determining the expanse of the alveolar surfaces; the volume of blood forced through the pulmonary artery is a chief factor in determining the expanse of the capillary surface. However greatly or abruptly either factor may fluctuate, an immediate equal fluctuation in the other factor results from the automatic air cell-capillary mechanism<sup>1</sup> discovered by Dunham, and the efficacy of external respiration is thereby conserved.

The practical significance of this organization may not be ignored. The chief obligation in the prevention of and treatment for intrathoracic diseases is to continue external respiration, measured by vital capacity, at its highest possible level during illness and to promote its rehabilitation during convalescence. This is particularly pertinent in primary abscesses which apparently arise exclusively in atelectatic lungs. Whether atelectasis is provoked by obstruction of a bronchus or by obstruction of a branch of the pulmonary artery, the circulation of the blood in the capillaries of the pulmonary vessel nearly ceases,<sup>2</sup> and the volume of blood (nutrient) supplied by the bronchial arteries is greatly reduced.

*Filtration of Inspired Air.*—Dust and bacteria floating in inspired air are so thoroughly removed by bronchial mucosa that in health they seldom, if ever, enter the terminal bronchioles and air cells. Larger foreign bodies, saliva, mucus, blood, pus, etc., after aspiration are arrested and commonly are expelled by peristaltic contractions of the bronchi. Sometimes coughing helps to impact foreign bodies and to force secretions into the air cells. Consequently, the small fraction of the ventilating surface extending from the trachea to the terminal bronchioles is constantly contaminated with virulent and avirulent bacteria, and at intervals these bacteria are forced into the air cells.

*Filtration of Pulmonary Arterial Blood.*—Blood delivered through the pulmonary artery frequently contains bacteria, perhaps always at the height of intestinal digestion. Bacteria, in part pathogenic, dead cells, foreign bodies and toxic substances are filtered from the blood

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1. Yates, J. L.: The Significance of Vital Capacity in Intrathoracic Therapy. Arch. Surg. **12**:257 (Jan. pt. 2) 1926.

2. Coryllos, P. N., and Birnbaum, G. L.: Circulation in Compressed, Atelectatic and Pneumonic Lung, Arch. Surg. **19**:1346 (Dec.) 1929.

by the endothelium of the capillaries. Presumably the aerating surface not only is constantly contaminated, but is subjected to physical and chemical injury.

*Filtration of Bronchial Arterial Blood.*—Blood delivered through the bronchial arteries provides the great bulk of the nutrition for the lungs and visceral pleura in man and other animals with thick pleurae. Bacteria are infrequent in systemic arterial blood except in terminal septiciemias, and those carried in the blood by the bronchial arteries are removed by the endothelium of the capillaries. Contamination of the nutritive surface is of little menace save in processes that are otherwise inevitably lethal.

Antibodies are elaborated by reticulo-endothelium in both blood circuits, in lymph glands, within the parenchyma and in the cells lining the alveoli.<sup>3</sup> Not only does the lung provide external respiration, but it is a main organ of defense. Hence pulmonary incapacity imposes two serious burdens.

#### CLINICAL ASPECTS

Peribronchial suppurations coincident with bronchiectasis and focal infections resulting from penetrating injuries being excluded, pulmonary abscesses occur as sequelae of acute and chronic (tuberculous) pneumonitis, as postoperative complications, as consequences of vascular and intracardiac thrombosis and, rarely, after direct and indirect trauma.

Pneumonitis results from bacterial invasion of an atelectatic and consequently a hyphemic lung. Abscesses develop secondarily when a portion of the inflamed lung is rendered ischemic by obstruction of a bronchial arteriole and liquefaction follows necrosis. The chief sources of invading bacteria are the ventilating and aerating surfaces. Primary pulmonary abscesses arise from the bacterial invasion of a portion of a lung rendered atelectatic by occlusion of a smaller bronchus or a branch of the pulmonary artery from embolism or from perivascular pressure exerted by a traumatic parenchymal hemorrhage resulting from rupture of a bronchial artery (splenization).

Smaller bronchi are occluded by mucus, blood, pus and foreign bodies, aspirated as a rule during operations on the mouth and upper air passages performed under general anesthesia. The air in the alveoli distal to the occlusion is soon absorbed, and the bacteria from the saliva, pathogenic aerobes and anaerobes are usually present to invade the atelectatic lung. If an abscess forms, necrosis predominates in the tissue reactions, and the pus gives off the characteristic fetor of so-called pulmonary gangrene. Embolic occlusion or hemorrhagic compression of a branch of the pulmonary artery produces atelectasis,

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3. Fried, B. M.: The Defensive and Metabolic Apparatus of the Lungs, Arch. Path. 6:1008 (Dec.) 1928.



because retraction of the capillaries likewise collapses the contiguous alveoli. It does not cause infarction in human lungs that are nourished by the bronchial arterial blood. If the embolus is bland or if, being contaminated, the bacteria are of little virulence, an abscess will not result unless the atelectatic portion is invaded by bacteria from its bronchus. Should the embolus carry virulent pyogenic cocci, an acute abscess develops; its walls are characteristically inflammatory, and the pus is not malodorous. Apparently, some abscesses primarily infected with pyogenic cocci are subsequently reinfected with the salivary organisms with the added consequences of this complication.<sup>4</sup>

*Prophylaxis.*—Earlier and more effective treatment for bronchitis, pneumonitis and pulmonary tuberculosis, utilization of local anesthesia in operations within the mouth and nasal sinuses and improved operative technic that has reduced the incidence of phlebitis have been effective in reducing the incidence of pulmonary abscess.

*Treatment.*—Whether abscesses are acute, subacute or chronic, single or multiple, or located near the hilus or periphery or in the intermediate zone, the therapeutic indications are the same: early drainage, collapse of rigid walls and restoration of the quality and quantity of the blood in circulation.

*Diagnosis.*—Recognition of the existence of an abscess is seldom difficult. Cough, expectoration of pus sometimes containing blood and

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4. A number of investigators have performed divers types of experiments in attempts to produce pulmonary abscesses under conditions simulating those affecting human beings. Animals with thin pleurae (dogs, cats, rabbits) have been employed, although Miller had shown that in these the circulation differed materially from that in the lungs of man. In animals with thin pleurae the pulmonary arterial blood supplies an effective proportion of the nourishment to the lung and visceral pleura. Consequently the data obtained from experimental observations cannot be applied directly to the pathogenesis of abscess in human lungs. Fortunately, the information obtained can be utilized in the main. The more significant facts follow: Bland emboli provoke no inflammatory response in the lung rendered atelectatic and consequently hyphemic. Contaminated emboli or bland emboli contaminated after deposition can provoke pneumonitis as well as abscess. Abscesses form in atelectatic lungs distal to emboli. As inflammation develops, the bronchial artery, being under vasomotor control, dilates and provides the usually defensive hyperemia in the portion of lung involved. Embolism in a pulmonary artery is a commoner cause of abscess than is bronchial occlusion or contamination with virulent bacteria. Abscesses initiated by pyogenic cocci are aggravated if bacteria from bronchi are added. A number of bacteria commonly resident in the saliva, not Vincent's *Fusospirochaetus* alone, can cause the chronic gangrenous abscesses and fetor. Holman, E., and Mathes, M. E.: Production of Intra-Pulmonary Suppuration by Secondary Infection of Sterile Embolic Area, *Arch. Surg.* **19**:1246 (Dec., pt. 2) 1929. Van Allen, C. M.; Adams, W. E., and Hrdina, L. S.: Bronchoscopic Contamination in Embolic Abscess of Lungs, *ibid.* **19**:1262 (Dec., pt. 2) 1929; Embolism in Bronchogenic Infection of Lung, *ibid.* **19**:1279 (Dec., pt. 2) 1929.

often fetid, pain, fever with and without chills and dyspnea, a day or two or several weeks after an acute infection of the respiratory tract, tonsillectomy, extraction of teeth, phlebitis or a clean surgical operation is indicative. Physical and roentgen examinations usually give conclusive evidence. Bronchoscopy may be helpful in determining the localization when the roentgenograms do not show the abscess.

Drainage of abscesses near the hilus is commonly spontaneous and if aided by posture is effective. Posture is determined by trial with each patient. Some are benefited by having the head elevated, others by having the feet elevated, some by lying prone on the back, others lying face downward and some by added turning to one side or the other. It has been claimed that bronchoscopy can be helpful in facilitating the drainage. This is disputable.

Smaller abscesses in the intermediate zone and in the periphery may not empty themselves in any posture. If allowed to persist, they tend to enlarge, to involve a larger pulmonary area and to become chronic, and may lead to such complications as septicemia, intracranial abscess, anemia, empyema, etc. Delay of treatment is too dangerous to be considered. The first and least radical step is to alter intrapulmonary tension, which, with posture, may promote drainage requisite to recovery. A temporary paralysis of the diaphragm<sup>5</sup> may be induced or an artificial pneumothorax employed. Opinions differ as to the advantages and disadvantages of the two methods. Induced temporary paralysis is safer, as it adds no danger of empyema, is applicable even when adhesions are present, requires but one procedure and is quite as efficacious as the other method.

A single abscess in the intermediate zone that persists in spite of the foregoing measures, can, if it is clearly visualized, be aspirated under the fluoroscope and, if necessary, drained with a small catheter. Empyema is not the danger it is alleged to be unless superficial abscesses are aspirated, but after such drainage patients should be watched. Prompt closed drainage in empyema is usually effective. This risk is preferable to more radical procedures with permanent reduction of vital capacity.

A single abscess or adjacent abscesses near the periphery should be drained exteriorly. If there are no adhesions between the overlying pleurae, a two-stage operation is needed to eliminate the danger of empyema.

Multiple abscesses, including tuberculous ones, that have not yielded promptly to the influence of posture and to the partial deflation and immobilization of the lung provided by induced paralysis of the diaphragm, with its attendant increased blood supply, in addition to

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5. Yates, J. L., and Raine, F.: Induced Paralysis of the Diaphragm, *Arch. Surg.* **21**:666 (Oct.) 1930.

proper nonoperative measures, including repeated blood transfusions, demand radical treatment if the patients are not to be irretrievably handicapped. When deflation of the affected portion of the lung has been proved inadequate, early collapse is required.<sup>6</sup> It is attainable by the abolition of intrapleural negative pressures through the induction and maintenance of suitable pneumothorax or by the excision of portions of the overlying ribs just adequate to produce the alteration in tension needed to promote healing.

Rarely is it necessary to remove enough ribs to cause collapse of an entire lung, unless intervention has been unduly delayed. Then excision should be attempted only on patients who are not beyond help, and should be performed in multiple stages. Partial thoracoplasty is often accomplished more safely in two or more stages. If the ribs are removed subperiosteally, immediate healing is apt to be smoother, but the ribs regenerate fantastically and refix the parietes sometimes detrimentally. If the intercostal muscles and the periosteum are removed with the ribs, the operation is no more burdensome and can be performed quite as expeditiously. If the skin flaps are not too large and are so fashioned as to preserve their blood supply, the healing is quite as satisfactory.

Subsequently, the parietes, consisting only of parietal pleura, panniculus and skin, are pliable and adapt themselves beneficially to changes in posture and to fluctuations in intrathoracic tension. One disadvantage must be recognized. If boneless parietes overlie the heart, it is subjected to atmospheric pressure, and if the myocardium is weakened, it may be unable to adapt itself to this burden.

Observations of three patients suffering from gangrenous abscesses and of one patient suffering from tuberculous abscesses are summarized to indicate avoidable mistakes and the efficacy of measures based on structure and function.

#### REPORT OF CASES

CASE 1.—R. C., a man, aged 28, was admitted to Muirdale Sanitarium on April 21, 1930. Tonsillectomy had been performed under general anesthesia in August, 1929. Within a month, there developed right-sided pleurisy, cough and dyspnea, followed by progressive loss of weight and strength. For the seven months preceding examination the sputum was blood-streaked; more recently, there was active hemoptysis. Cough was the most prominent symptom. The tentative diagnosis was tuberculosis with effusion at the base of the right lung. There was moderate secondary anemia; leukocytes numbered 22,000, with 82 per cent neutrophils, and there was a pronounced reaction to tuberculin. Although the sputum contained no tubercle bacilli, routine treatment was continued. On Nov. 11, 1930, the patient had a brisk hemorrhage followed by the expectoration of a large amount of foul

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6. Pulmonary deflation is proportionate to the extent of reduction in intrapleural negative pressure. Collapse is produced by the abolition of negative pressure; therefore, by atmospheric pressure. Compression results from the exertion of positive pressure, i. e., pressure in excess of atmospheric pressure.

pus. Constant cough was recorded, and on December 13 he had a profuse hemorrhage. The patient was presented at a staff conference on December 17, and although he was in a critical condition immediate nerve blocking and transfusion were advised; if these were successful, thoracoplasty was not to be delayed.

The right phrenic nerve was resected on Dec. 18, 1930, to induce permanent paralysis; exeresis was contraindicated because of adhesions, and a transfusion of 500 cc. of unmodified blood was given. Postural drainage was begun, but was discontinued on December 24 because of hemorrhage, although hemorrhages had been frequent previously without postural provocation. On February 25, the patient was given neoarsphenamine intravenously without benefit, and this procedure was repeated later. Cough continued, and sometimes there was bloody sputum. On February 24, it was agreed at a staff conference that if improvement did occur,



Fig. 1 (case 1).—Seven months after onset of abscess in lower lobe of right lung.

thoracoplasty should be attempted, although the patient was wofully weak. Improvement followed, however. The patient has been afebrile from March 23, 1931, to the time of this report, with a pulse rate of from 80 to 100. He is able to take limited exercise. Expansion of the right side of the chest is limited, but is improving.

Figure 1 shows the chest on the patient's admission to the hospital and figure 2 the condition eight months later, as it was at the time of induced paralysis of the right side of the diaphragm on Dec. 18, 1930, and figure 3, taken on April 11, 1931, shows the condition as it is at the time of this report.

*Comment.*—If the patient had been properly treated immediately after admission to the sanatorium instead of after a delay of seven months, he would have recovered more rapidly than he has, since his

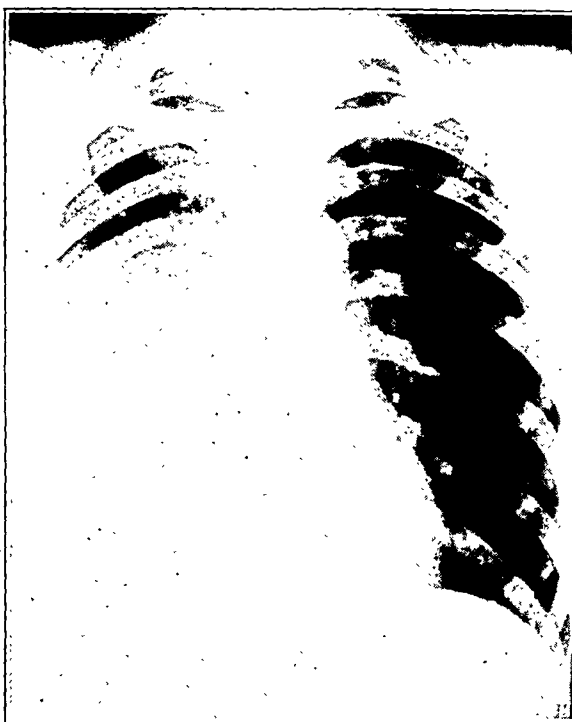


Fig. 2 (case 1).—Fifteen months after onset of abscess in lower lobe of right lung and just before paralysis of right side of diaphragm was induced.



Fig. 3 (case 1).—Nineteen months after onset of abscess in lower lobe of right lung, four months after paralysis of right side of diaphragm was induced, and one month after the patient became afebrile.

diaphragm was paralyzed eight months later, and with less permanent disability. A mistaken diagnosis, natural in an institution for patients suffering from pulmonary tuberculosis, was largely responsible for procrastination. Since weekly staff conferences are being held at which the records of all patients are reviewed, and those of all patients not progressing satisfactorily are reviewed repeatedly, mistakes are being eliminated. The slight alteration in intrathoracic pressure resulting from phrenicectomy initiated recovery. It is questionable whether neoarsphenamine, administered intravenously, was a contributing factor. There was no proof that the fetid sputum contained *Fusospirochaetus* or that the organisms disappeared because of the drug.

CASE 2.—E. G., a white woman, aged 24, was admitted to Muirdale Sanitarium on May 23, 1930. Six months previously, her tonsils and adenoids had been removed under ether anesthesia. Two weeks later, cough and hemoptysis and several large and repeated smaller hemorrhages were noted. The patient had lost in weight and strength and had been incapacitated for ten weeks. Extensive involvement of the right lung with cavities in the upper two-thirds had developed in the four months since a diagnosis was obvious. The temperature was 102 F.; the pulse rate, 100, and respirations, 24. There was moderate secondary anemia; the leukocytes numbered 14,500, with 71 per cent neutrophils, and sedimentation was rapid (56 per cent). The tentative diagnosis was multiple abscesses of the right lung. Acute pleurisy pain developed on May 29, followed by bloody expectoration. Between June 2 and June 23, the patient was given 4,050 cc. of air in seven sittings, which finally produced positive intrapleural pressure. Adhesions prevented satisfactory collapse. Conditions were little altered and certainly not improved. Temporary paralysis of the right side of the diaphragm was induced on July 10, and a transfusion of 500 cc. of unmodified blood was given. The cough was aggravated by the operation; the sputum was voluminous and foul. On July 18, the condition was ameliorated by a withdrawal of 400 cc. of air. On August 23, the postero-lateral portions of the sixth, seventh, eighth and ninth ribs and intercostal muscles were removed, and the patient was given 500 cc. of unmodified blood by transfusion.

Convalescence was uncomfortable. Drainage was freer when the patient was prone and on her right side. During September and October, cough and expectoration diminished and were slight when she was discharged on the last day of November. She was observed at intervals after discharge, and continued improvement was noted. She was last seen on April 18, 1931. She had regained strength and was overweight; there was dyspnea on overexertion; the lung was resonant throughout; there was slight limitation of expansion of the right side of the chest. Motion of the right side of the diaphragm was incompletely recovered. The vital capacity was 65 per cent, which would increase as the diaphragm regained motion; the low value was due in part to the fact that she was overweight. The blood showed no anemia; the sedimentation rate was 108 per cent.

Figure 4 shows the involvement of the lung on the patient's admission; figure 5, after pneumothorax had been started; figure 6, four days after temporary nerve block with incomplete paralysis of the right side of the diaphragm (rise of diaphragm prevented by pneumothorax); figure 7, nineteen days after partial thoracoplasty; figure 8, fifty-four days after partial thoracoplasty, and figure 9, two hundred and fifty days after partial thoracoplasty. Motion of the diaphragm was incompletely recovered.

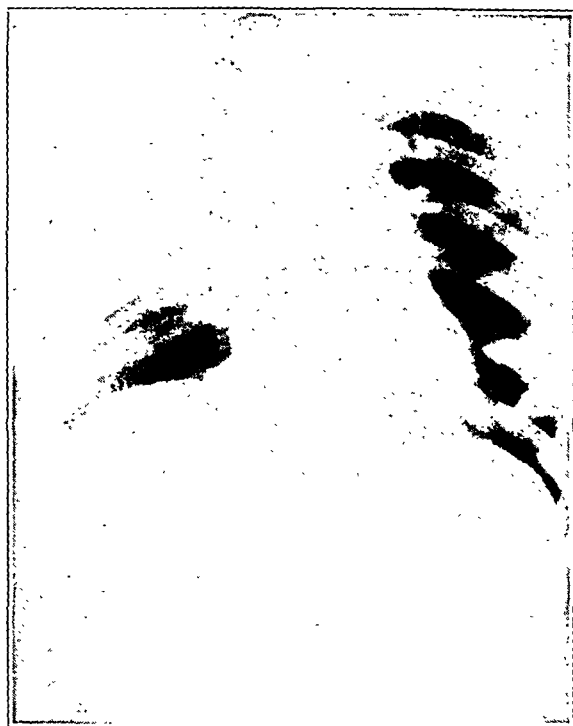


Fig. 4 (case 2).—Five and one-half months after onset of multiple abscess in the middle and upper lobes of the right lung.

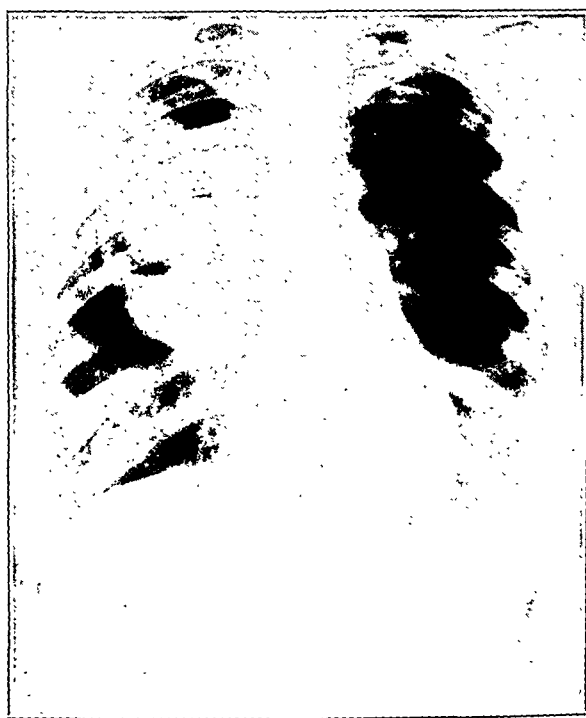


Fig. 5 (case 2).—Six months after onset of multiple abscesses. The patient had received three injections of 1,650 cc. of gas. The fluid levels in the abscess cavities are revealed.

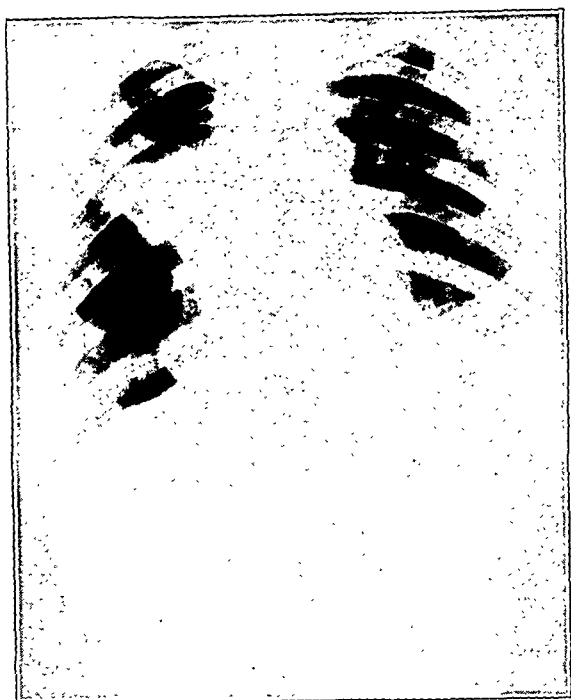


Fig. 6 (case 2).—Seven months after onset of multiple abscesses, four days after temporary induced paralysis and before aspiration of air. Positive intrapleural pressure prevented rise of diaphragm.



Fig. 7 (case 2).—Ten months after onset of multiple abscesses and nineteen days after resection of the posterolateral aspects of the sixth, seventh, eighth and ninth ribs and intercostal muscles.



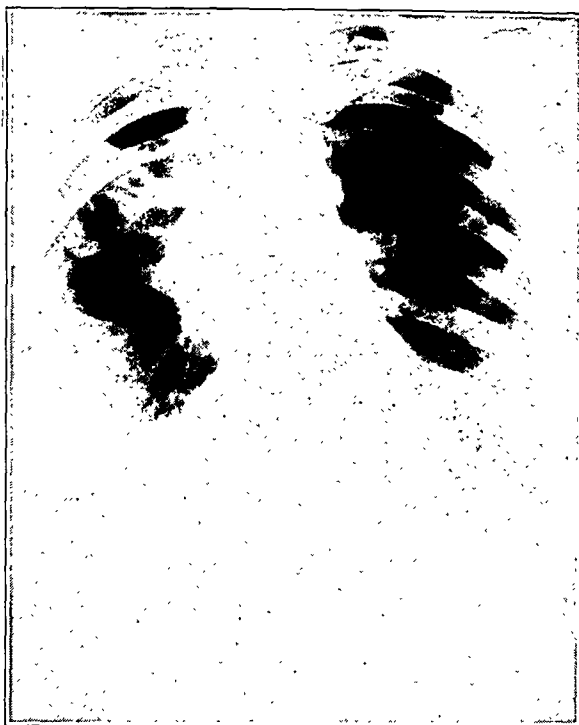


Fig. 8 (case 2).—Eleven months after onset of multiple abscesses and fifty-four days after partial thoracoplasty.

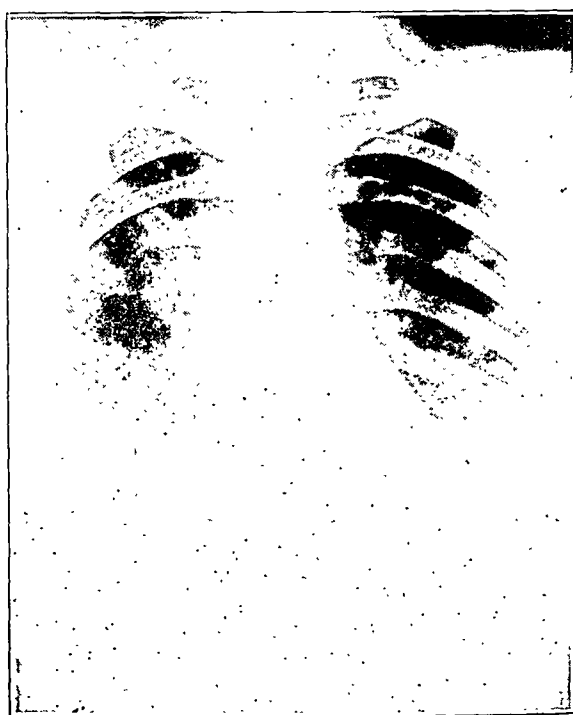


Fig. 9 (case 2).—Sixteen months after onset of multiple abscesses, and two hundred and fifty days after partial thoracoplasty.

*Comment.*—Artificial pneumothorax might have brought recovery had adhesions not prevented retraction of the lung. Had the induced positive intrapleural pressure disrupted the adhesions, empyema could have been produced, which, complicated by the pneumothorax, would have been dangerous. Six months elapsed after the onset of symptoms of abscess before a diagnosis was made. A temporary paralysis of the diaphragm induced soon after onset could have promoted a rapid recovery. A permanent induced paralysis of the diaphragm would have imposed an irremediable and unwarranted reduction in external respiration, a handicap that would have restricted activities throughout life.



Fig. 10 (case 3).—Abscess of the lower lobe of the right lung (gangrenous; of two and one-half months' duration). Empyema of (?) weeks' duration.

The partial thoracoplasty, limited to the amount of alteration in intrapulmonary tension needed to permit of healing, is illustrative of similar procedures equally applicable to certain patients suffering from chronic tuberculous abscesses. Cavitations restricted to the upper or the lower segments of the lung when the balance of the lung is healthy can be induced to collapse and heal by removal of only the overlying ribs; thus the balance of the lung is preserved for respiration and other functions.

CASE 3.—W. H. H., a white man, aged 54, was admitted to Muirdale Sanitarium on Nov. 16, 1929. He was so deaf and so weak that a history was unobtainable. Apparently, he had been well until about three months previously. At that time he had an acute infection of the respiratory tract, during which a sudden sharp

pain in the right side of the chest was followed by a high temperature. He improved for a week or two, when paroxysmal attacks of coughing began and continued. The sputum was profuse and fetid, but not bloody.

Pulmonary gangrenous abscess with empyema was recognized. Operation was deferred, as postural drainage was effective and the empyema was encapsulated. Four days later, the sputum contained blood, and thereafter hemoptysis continued. On November 16, exeresis was performed because crushing of the right phrenic nerve failed to induce complete paralysis. A segment of the ninth rib was resected, revealing a gangrenous pleuropulmonary abscess, which was drained. The patient weakened progressively; there was no manifest healing, and he died on December 13.

Figure 10 was taken on November 19. There was empyema, the fluid level suggesting connection with a bronchus.

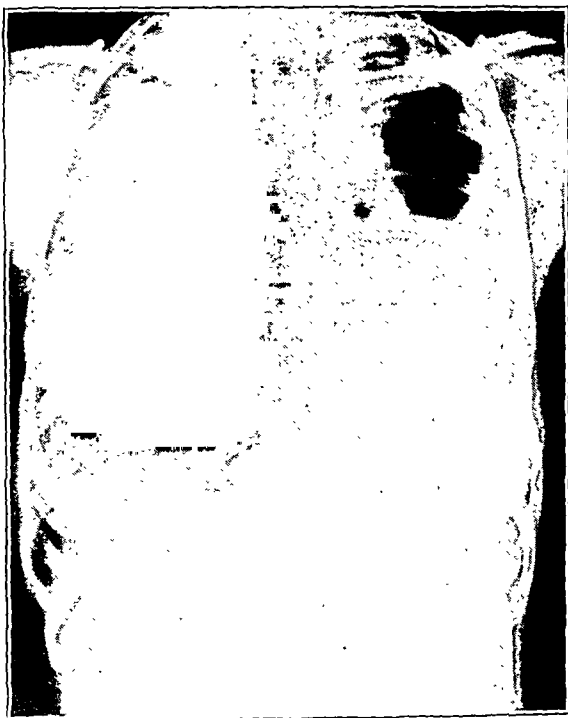


Fig. 11 (case 4).—Thirty-four months after onset, twenty-four months after the first and ten months after the last administration of gas, and one month before exeresis of the left phrenic nerve. Residual pneumothorax had persisted for ten months.

*Comment.*—It is questionable whether a weakened, discouraged man, old beyond his years, would have recovered even if a diagnosis might have been made immediately and treatment been given promptly. Delay forfeited what chance there might have been. At the time of operation, the patient's power of repair was so dissipated as to preclude recovery.

CASE 4.—E. V. V., a white woman, aged 32, was admitted to the hospital on March 12, 1924. She had been well until five months previously, when a severe cold preceded a left-sided pleurisy. Afternoon fever, chills and loss of weight and strength continued until she was incapacitated. The right lung contained a healed apical lesion; the left lung, fibrocaseous lesions throughout with cavitation in the upper portion. The sputum contained many bacilli.

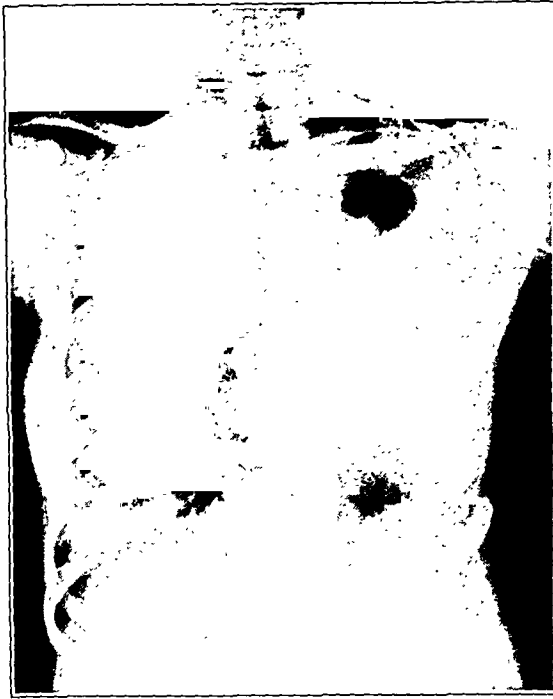


Fig. 12 (case 4).—Forty months after onset, sixteen months after the last administration of gas and five months after exeresis. Some pneumothorax still persists; the left part of the diaphragm is materially elevated, and compensatory emphysema is manifest in the right lung. The picture was taken after the second stage of thoracoplasty begun four months previously.



Fig. 13 (case 4).—Fifty-two months after onset and seventeen months since exeresis. The picture was taken after thoracoplasty begun sixteen months previously had been completed and two months before portions of regenerated ribs were excised so that the patient might sleep on her left side and be free from pain.

Between Sept. 29, 1924, and Nov. 12, 1925, pneumothorax was employed twelve times, with a total insufflation of 4,900 cc. of air. In February, 1925, a rise in temperature and hydrothorax were noted; the effusion had occurred previously but without fever. On Oct. 12, 1926, an exeresis of the left phrenic nerve produced a paradox. On Nov. 11, 1926, the first stage of thoracoplasty was done, which was completed in four operations with three transfusions of unmodified blood. At the final operation, on May 24, 1928, portions of regenerated ribs were removed because they interfered with motion of the scapula, prevented the patient's sleeping on her left side and were painful. She was dismissed from the sanatorium on Jan. 24, 1929. The left lung was not functioning. The right lung, aside from compensatory emphysema, was normal. She remained well. When reexamined on Sept. 12, 1930, the condition of the lungs was found to be unchanged; her blood was in excellent condition; the lymphocyte-monocyte ratio was 0.35; the sedimentation values, 105 per cent.

Figure 11 shows the residue of pneumothorax present, the diaphragm being unparalyzed; figure 12, the condition after the second stage of thoracoplasty, and figure 13, thoracoplasty completed, with regeneration of the ribs.

*Comment.*—Experience proved that this patient was saved only by operation. Could this have been known at the time of her admission to the sanatorium, she could have been saved at least two years of treatment, and possibly more, as her condition then would probably have warranted more extensive operations at shorter intervals. The regeneration of ribs that occurred because the periosteum was not excised was undesirable in producing fixation.

#### SUMMARY

The pathogenesis of remediable forms of pulmonary abscess that develop in the lungs of human beings and also effective methods for prevention and treatment are established by recognizing the pulmonary structure and function peculiar to man and to other animals with thick pleurae.

The most efficacious means to prevent abscesses are: the employment of local anesthesia in the performance of operations on the mouth and accessory sinuses, notably the removal of tonsils and adenoids, except in children; the utilization of such surgical technic as will minimize post-operative phlebitis; earlier introduction of operative adjuncts in the treatment for pulmonary tuberculosis, and the prompt bronchoscopic removal of aspirated foreign bodies.

Treatment for pulmonary abscess, particularly for the more severe gangrenous form, will be more efficacious, especially in the restoration of external respiration, if appropriate measures that will promote adequate drainage are utilized as soon as posture alone is found to be inadequate.

# TRANSPERITONEAL SEMINAL VESICULECTOMY

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Since the first seminal vesiculectomy was reported by Ullmann in 1890, comparatively few surgeons of large experience have had the opportunity to perform this operation. In general, the accepted methods of surgical approach to the seminal vesicles are divided into two main classes: the perineal and the suprapubic extraperitoneal operations. Numerous modifications<sup>1</sup> have been devised in an attempt to overcome some of the difficulties and disadvantages of both of these methods. It is obvious that both the abdominal extraperitoneal operation and the operation by the perineal route require extensive dissection and, as a result, the laying open of large raw surfaces to infection from the already inflamed vesicles (Villard<sup>2</sup>). Furthermore, both of these operations are technically difficult, and several times have had to be abandoned because the vesicles could not be reached or properly exposed (Walker,<sup>3</sup> Weir,<sup>4</sup> Baudet and Kendirdjy<sup>5</sup>). Platon and Béloséroff, operating on cadavers, several times were unable to expose the seminal vesicles by the suprapubic extraperitoneal route.

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From the Surgical Division of the Montefiore Hospital, Dr. Harold Neuhof, director.

1. (a) Crouse, H.: An Improved Technique in Dealing with the Seminal Vesicles, *Urol. & Cuntan. Rev.* **21**:301, 1917. (b) Pauchet, V.: Extirpation des voies spermatiques dans la tuberculose génitale, *Rev. prat. d. mal. d. org. génito-urin.* **6**:200, 1909-1910; cited in *Ann. d. mal. d. org. génito-urin.* **28**:838, 1910. (c) Luys G.: *Maladies des vésicules séminales*, Paris, Gaston Doin, 1930, p. 242. (d) Schede, M.: Wegen Tuberculose extirpierten Hodens mit zugehörigen Samenstrang nebst Samenblase, *Deutsche med. Wchnschr.* **20**:161, 1894. (e) Squier, J. B.: Indications for Operation on the Seminal Vesicles, *Boston M. & S. J.* **170**:908, 1914. (f) Villard: Vasovésiculectomie par voie haute, *Lyon chir.* **3**:306, 1910. (g) Villeneuve: Epididymovésiculectomie dans la tuberculose testiculaire, *Marseille méd.* **28**:641, 1891. (h) Voelcker, F.: *Chirurgie der Samenblasen* (Neue deutsche Chirurgie), Stuttgart, Ferdinand Enke, 1912, vol. 2. (i) Young, H. H.: Ueber ein neues Verfahren zur Extirpation der Samenblasen und der Vasa deferentia, *Arch. f. klin. Chir.* **42**:456, 1900; (j) A Perineal Method for Excising or Draining the Vesicles, *Th. Am. A. Genito-Urin. Surgeons* **7**:73, 1912.

2. Villard: Deux cas de vaso-vésiculectomie pour tuberculose, *Lyon méd.* **108**:739, 1907.

3. Walker, G.: Tuberculosis of the Vesiculæ Seminales, Testes and Prostata, *Maryland M. J.* **44**:55, 1901.

4. Weir, R. F.: Cases in Genito-Urinary Surgery, *M. Rec.* **46**:163, 1894.

5. Baudet, R., and Kendirdjy, L.: De la vaso-vésiculectomie dans les cas de tuberculose génitale, *Rev. de chir., Paris* **34**:380, 1906.

In many of the seminal vesiculectomies that have been reported as successful, the actual extirpation was a blind procedure in the depths, consisting in more or less bluntly tearing out and curetting the vesicles. In such cases, there is the obvious danger of postoperative hemorrhage from an inaccessible source.

Urinary fistula has frequently occurred following the perineal operation.<sup>6</sup> This is not always due to direct injury of the urinary tract, but may result from sloughing of the urethra following incision or enucleation of the prostate or from the opening of an abscess cavity already communicating with the urinary passages. A few investigators (Colston,<sup>7</sup> Bidgood, Young) have tried to explain the urinary fistula on the basis of a leak through the cut ends of the indurated ejaculatory ducts. In Colston's case of simple epididymectomy, urine escaped through the ejaculatory ducts and was into an inguinal fistula. However, the fact that urinary fistula has not been seen following the suprapubic extraperitoneal operation speaks against this explanation.

Furthermore, in the perineal operation, tearing or cutting into the rectum may occur (Young,<sup>8</sup> Fuller.<sup>9</sup>) Another drawback of this operation is the difficulty of resecting the easily avulsed vas deferens.

The ischiorectal procedures requiring excision of the sacrum and coccyx (Schede,<sup>1a</sup> Bolton,<sup>10</sup> Choltzoff<sup>6a</sup>) produce shock, while the suprapubic T-shaped incision of Young<sup>11</sup> has been abandoned by its original proponent because of the unsatisfactory results and the high mortality; two of his three patients died. At present, the consensus

6. (a) Choltzoff: *Traitement opératoire de la tuberculose des canaux déférents et des vésicules séminales*, Ann. d. mal. d. org. génito-urin. **27**:1121, 1909; translated from *Praktischeskaia Meditzina*, January, 1909. (b) Marion, G.: *Castration avec ablation de la prostate en cas de tuberculose génitale*, Soc. de chir., June, 1909; cited in Ann. d. mal. d. org. génito-urin. **28**:847, 1910. (c) Pauchet (footnote 1 b). (d) Ullmann, E.: *Extirpation tuberkulöser Samenbläschen*, Zentralbl. f. Chir. **17**:137, 1890. (e) Walker (footnote 3). (f) Weir (footnote 4).

7. Colston, J. A., quoted by Young, H. H., and Davis, D. M.: *Young's Practice of Urology*, Philadelphia, W. B. Saunders Company, 1926, vol. 1, p. 170, and vol. 2, p. 530.

8. (a) Young, H. H.: *Genital Tuberculosis with Especial Reference to the Seminal Vesicles*, Ann. Surg. **34**:601, 1901; (b) *Presentation of a Radical Operation for Tuberculosis of the Seminal Tract*, Surg., Gynec. & Obst. **26**:375, 1918; (c) *Tuberculosis of the Seminal Tract*, Arch. Surg. **4**:334 (March) 1922.

9. Fuller, E.: *Seminalvesiculotomy*, J. A. M. A. **59**:1959 (Nov. 30) 1912; *Surgery of the Seminal Vesicles*, New York M. Rec. **87**:134, 1915; *Operative Surgery Applied to the Seminal Vesicles*, *ibid.* **65**:807, 1904.

10. Bolton, P. R.: *The Operative Routes to the Seminal Vesicles*, J. Cutan. & Genito-Urin. Dis. **17**:551, 1899.

11. Young, H. H.: *Suprapubic Retrocystic Extraperitoneal Resection of the Seminal Vesicles, Vasa Deferentia, and Half the Bladder*, Ann. Surg. **32**:557, 1900.

favors the perineal operation (Marion,<sup>6b</sup> Pauchet,<sup>1b</sup> Young,<sup>12</sup> Cunningham,<sup>13</sup> Morrissey<sup>14</sup>), which usually has the advantage of better surgical exposure, more direct drainage and a lower mortality. However, the perineal route affords considerable hardship and dangers (urinary and rectal injury) when used by surgeons who have not had mature experience in this field. Furthermore, larger abscesses or cysts of the seminal vesicles may not be adequately exposed because of the smallness of the operative field.

Recently, when I was confronted with the problem of excision of a moderately large chronic abscess of the seminal vesicles, it appeared that the chance of total extirpation without spilling of pus, by the usual perineal or suprapubic operations, was poor. Therefore, I approached the seminal vesicles through a free intraperitoneal incision, retracting the emptied bladder forward, and thoroughly packing off the intestines. The domelike upward bulging of the enlarged seminal vesicles between the bladder and the rectum was immediately seen. A transverse incision was made in the peritoneum over the dome, and the posterior surface of the seminal vesicles was freed by sharp dissection. The vasa deferentia were isolated and divided between ligatures. The anterior surface of the vesicles was then separated from the bladder with the scalpel, and the abscess was completely extirpated. It is especially to be emphasized that the exposure was more than adequate, the dissection having been done entirely under vision. All blood vessels were clamped and ligated, leaving a dry field. Drainage was provided transperitoneally by means of a rubber dam and one gauze packing in the lower end of the abdominal wound. The postoperative course was smooth, save for a slight transient gastric dilatation on the second day after operation and a mild attack of herpes zoster four weeks later. Thick, fecal-smelling pus drained for one week through the lower end of the abdominal wound. The skin and muscle of the lower half of the incision separated on the tenth day, healing by secondary intention with adhesive strapping. The pus became scanty after irrigation with surgical solution of chlorinated soda, but because of the long tract, a thin tube was left *in situ* for more than a month. In retrospect, this period is realized to have been unnecessarily long. The patient's general condition quickly improved, and he is now practically symptomless, save for occasional slight precordial pain.

12. Young (footnote 1 i; footnote 8 c).

13. Cunningham, J. H., Jr.: Technique for Drainage or Excision of the Seminal Vesicle, *Surg., Gynec. & Obst.* **24**:487, 1917.

14. Morrissey, J. H.: Chronic Seminal Vesiculitis and Prostatitis: Further Report on Results of Operative Treatment and Its Indications, *Arch. Surg.* **15**: 102 (July) 1927. Morrissey, J. H., and Smith, F. W.: Surgery of the Seminal Vesicles, Indications, Technique and Results, *Surg., Gynec. & Obst.* **37**:480, 1923.



## REPORT OF A CASE

*History.*—A man, aged 47, was admitted to the medical service of Dr. B. S. Oppenheimer at the Montefiore Hospital on Feb. 7, 1931, complaining of dyspnea, and pain in the chest, over the precordium, in the shoulders and in the joints of the hands. He said that he had not had gonorrhea.

He was first a patient at the Mount Sinai Hospital, where he was admitted on three separate occasions between September, 1928, and September, 1930. He complained of asthenia, cardiac distress, fever and severe pain in his shoulders, hands and knees. The joints were neither red nor swollen, but were very tender. The pain in the hands and fingers was so severe that he was unable to work. He had bilateral pleural effusion, enlarged liver and spleen and frequently a pericardial friction rub. Evidence of a valvular lesion was inconstant. Roentgenologically, the heart appeared normal in size. Two weeks after admission, epididymitis developed on the left side, which took about five weeks to subside. Since then, he has complained of urgency and frequency of urination. In 1928 he was considered to present a case of acute rheumatic fever, polyserositis, mitral stenosis and insufficiency and aortic insufficiency.

On his second admission, six months later, he complained, in addition, of nocturia, dysuria and frequency of urination. He also had pain in both shoulders and over the spine. At that time, the only cardiac symptoms remaining were those of slight reserve. The left ventricle was enlarged, and he had a mild cystitis. The x-ray film showed spondylitis and a small concretion near the lower part of the right ureter, which had the appearance of a calculus. The electrocardiogram revealed left ventricular preponderance. Cultures of urine from the right and left ureters were sterile. After a stay of ten days in the hospital, he was discharged with a diagnosis of acute nasopharyngitis, spondylitis and cystitis.

On the patient's last admission, after two years of observation, the cardiac symptoms were unchanged. He complained of steady, dull, nonradiating pain in the left subcostal region and vague pains in the joints. He was dyspneic and orthopneic, but not acutely distressed. A systolic murmur was heard replacing the first sound throughout the precordium. There was tenderness over the left subcostal region, and evanescent redness was noted over the interphalangeal joints. The prostate was described as boggy and enlarged. His discharge note read as follows: "The presence of a bilateral pleurisy, spondylitis and subacute left pyelonephritis and cystitis on the left side were fairly obvious. It was difficult, however, to evaluate the arthralgias and myalgias, which were associated with cutaneous lesions over the right leg, which appeared to consist of injected capillaries, which blanched incompletely, and might be manifestations of an aberrant acute rheumatic fever. The cardiac syndrome, also, was a problem because of the absence of electrocardiographic evidence and of any murmurs associated with rheumatic carditis. It was assumed that two factors were present: the atherosclerosis, as inferred from the peripheral manifestations, and the rheumatic element, inferred from the history of polyserositis and cardiac murmurs. There was improvement in all his symptoms but the urinary. He suddenly developed gross hematuria, which, on cystoscopy, was found to be due to diffuse hemorrhagic cystitis. This persisted until the time of his discharge, and he was referred for genito-urinary treatment."

After leaving the hospital at the end of September, 1930, the patient tired very easily and he had precordial and articular pains and urinary symptoms. He visited numerous clinics and hospitals, and cystoscopy was performed several times. He suffered from epididymitis on the right side shortly afterward.

At the time of his admission to the Montefiore Hospital, the heart showed few signs, except diminished reserve and a left ventricular enlargement, the latter being confirmed by the electrocardiogram and roentgen examination. The urine contained many white blood cells. Moderate anemia was found, the hemoglobin varying between 65 and 60 per cent. The blood pressure was 94 systolic and 62 diastolic. Blood urea nitrogen was 13.3 mg. per hundred cubic centimeters, and the Wassermann reaction was negative. Both epididymes were thickened and contained hard nodules.

On rectal examination, a soft, rounded, cystic mass was felt at the upper border of the prostate. This was thought to be a cyst or abscess of the prostate, utricle or seminal vesicle. Following several vigorous massages over this mass, no secretion was obtained. Cystoscopy gave negative results, save for slight



Fig. 1.—Seminal vesiculogram taken one day after injection into vas.

cystitis. Both ureters were catheterized without obstruction. A small shadow, seen lateral to the coccyx on previous roentgenograms, was shown to be outside the right ureter. A cystogram was normal.

On March 8, 1931, with the patient under local anesthesia, a preliminary bilateral vasectomy was done. Two cubic centimeters of lipo-iodine Ciba was injected into the proximal end of the right vas deferens, but, after the injection of 0.25 cc. into the left vas, an obstruction to the passage of the oil was encountered. Seminal vesiculograms (figs. 1 and 2), taken one and four days following the injection into the vas, showed an enlargement of the vesicles to about three times their normal size and a loss of their anatomic structure. An obstruction was seen in the left vas. A diagnosis of abscess of the seminal vesicles was made. Since the patient had the symptoms and signs of toxic absorption (a subfebrile course, asthenia, anemia, myalgia and arthritis), and because the vesicles could not be emptied by massage, the obvious next step was to remove operatively this focus of infection in the seminal vesicles.

*Transperitoneal seminal vesiculectomy.*—Operation was performed on April 8, 1931. With the patient under spinal anesthesia (procaine hydrochloride), a 12 cm. midline incision in the lower part of the abdomen was made. In marked Trendelenburg position, the peritoneum was opened the full length of the incision, and the intestines were carefully packed off. The empty bladder was grasped by a ring clamp and retracted forward. A domelike swelling under the peritoneum, an abscess of the seminal vesicles, was seen posteriorly at the base of the bladder, between it and the rectum. A transverse incision was made through the peritoneum over the dome. The peritoneum was easily dissected back from the underlying seminal vesicles. Both vasa deferentia with their blood vessels were identified, and were cut between ligatures. By traction on the stumps of the vasa the anterior surface of the seminal sac could be exposed at its upper attachment to



Fig. 2.—Seminal vesiculogram taken four days after injection into vas.

the bladder. The seminal vesicles were then freed from their attachment to the bladder by scalpel dissection and completely removed. Bleeding points were clamped and ligated, a dry field being left, save for slight oozing. One thin gauze packing and a rubber dam drain were brought out transperitoneally through the lower angle of the abdominal incision. The incision was closed in layers in the usual manner.

*Pathologic Report.*—Macroscopic Examination: The specimen (fig. 3 *A*) consisted of the enucleated seminal vesicles fused into one markedly enlarged sac, measuring 5 by 3.5 by 2 cm., with 2.5 cm. of the right and 1 cm. of the left vas deferens attached. On sagittal section (fig. 3 *B*), the center was seen to be composed of very friable, loosely adherent, necrotic, yellowish-brown granular material. The surrounding wall was made up of a very dense fibrous tissue, measuring from 3 to 5 mm. in thickness. The vas was slightly enlarged, measuring 7 mm. in diameter. Its wall was densely fibrotic, and in one portion contained

a soft, brownish, liquid material (lipo-iodine), which appeared fairly well encapsulated. Sections of the seminal vesicle were taken for microscopic examination.

**Microscopic Examination:** A section composed of loose connective tissue, smooth muscle and glandular elements was examined. There were several large, irregular, cystic dilatations of flattened epithelium lining the cysts. The cysts were filled with a pink-staining material, which was probably some injected substance (lipo-iodine). The interstitial tissue showed only an occasional scattering.

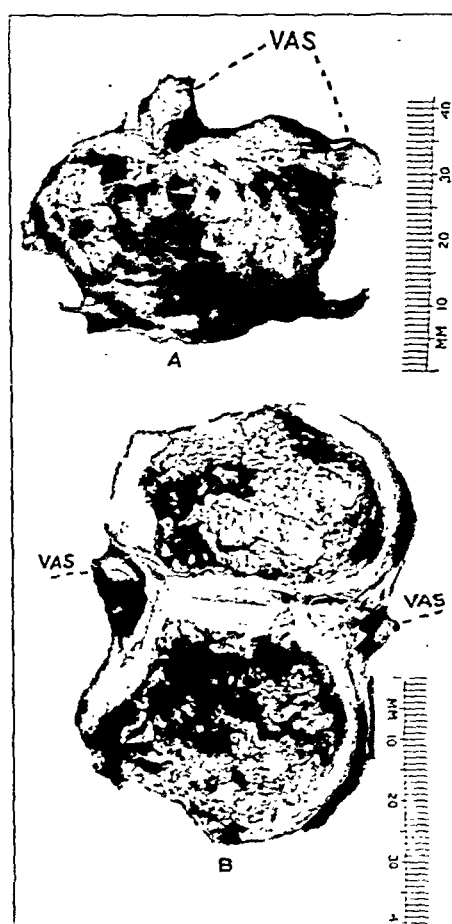


Fig. 3.—*A*, specimen showing removed seminal vesicles with attached stumps of both vasa deferentia. *B*, sagittal section of seminal vesicles. Note that both vesicles had fused into one abscess cavity.

of lymphocytes. The surrounding tissue in these areas was markedly edematous. Section through the wall showed a marked degree of inflammation on the surface, deposition of fibrin, lymphocytes, cellular debris, red blood cells and occasional polymorphonuclears. In places, beginning organization was present. Large numbers of fatty cells were present just beneath the inflamed area.

**Diagnosis:** Sections through the vas deferens and seminal vesicle showed subacute vesiculitis.

Specimens consisting of small pieces of the vas deferens appeared normal and microscopically showed no pathologic change.

Culture of pus taken from the seminal vesicles immediately following operation showed *Bacillus coli*.

*Postoperative Course.*—This was eventful, but progress was steady, save for a slight gastric dilatation on the second postoperative day, lasting about twenty-four hours. Though the upper half of the wound separated down to the peritoneum on the tenth day, there was no interruption in general improvement. The rubber dam and gauze drains were removed and replaced by a thin calibered tube, through which the tract was irrigated three times a day with surgical solution of chlorinated soda. The wound was strapped with adhesive tape and was practically healed after six weeks. Because of the long drainage tract, the tube was left *in situ* for five weeks, being gradually shortened. It is my impression that three weeks would have sufficed, but because of inexperience with this operation, it was deemed wise to maintain the sinus for a longer time. There was profuse drainage of fecal-smelling pus for one week, which rapidly diminished following the irrigations with surgical solution of chlorinated soda. The sinus healed promptly after removal of the tube, and the patient was able to walk about forty days after the operation. An interesting complication, a left lumbar herpes zoster, was noted four weeks after spinal anesthesia was administered, at the same level. The articular and spinal pains, severe before operation, had disappeared. The patient still complained of slight precordial distress on exertion and very much diminished pain in the shoulder muscles. His general condition was greatly improved when he was discharged from the Montefiore Hospital on June 3, 1931.

The report of this case is believed to represent the first recorded case of transperitoneal seminal vesiculectomy, in which diagnosis was made preoperatively by physical examination and seminal vesiculography, and the patient was operated on by preconceived plan. Though Guiteras<sup>15</sup> once operated transperitoneally on a large cyst, which he considered as probably originating from the right seminal vesicle, he was unable to enucleate the mass and was content with simple drainage.

The transperitoneal approach afforded more than adequate exposure, allowing the entire operation to be done under vision. All blood vessels could be clamped and ligated. Abscesses and cysts of larger size, which cannot be sufficiently exposed by the perineal or suprapubic extraperitoneal routes, could much more easily be removed by the transperitoneal operation.

Two disadvantages of transperitoneal seminal vesiculectomy immediately become obvious; first, the danger of spilling pus, with consequent peritonitis, and, second, the length and curve of the drainage tract.

It must constantly be borne in mind that opening of the peritoneum always carries with it a real potential danger. Therefore, even with careful technic and the avoidance of gross contamination with pus, one might hesitate to approach transperitoneally an acutely infected or tuberculous seminal vesicle. It should be remembered, however, that in the suprapubic extraperitoneal operation the peritoneum often is

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15. Guiteras, R.: A Case of Seropurulent Cyst, Probably of the Right Seminal Vesicle, *Lancet* 2:74, 1894.

inadvertently torn (Walker,<sup>3</sup> Weir,<sup>4</sup> Baudet and Kendirdjy<sup>5</sup>), and, in addition, large extraperitoneal raw surfaces are exposed to infection. In the various approaches from below, though the peritoneum has only rarely been opened, extensive dissection is also required, and urinary and rectal injuries are not at all uncommon. Since the great majority of seminal vesicular infections, aptly named by Belfield<sup>16</sup> "pus tubes in the male," are of long standing before operation is indicated, we usually find a low grade infection or sterile pus. In such cases, and for cysts and neoplasms of the seminal vesicles, it would certainly seem that the transperitoneal route offers the greatest advantages.

In the postoperative treatment of my patient, the disadvantage of a long transperitoneal drainage tract was appreciated, the sinus having been kept open for an unduly long time. Though the end-result was good, other methods of drainage, such as the perineal or lateral abdominal, deserve consideration.

#### CONCLUSIONS

1. In a case of colon bacillus abscess of both seminal vesicles, the diagnosis was made preoperatively by rectal examination and seminal vesiculography. The symptoms and signs were those of absorption from a low grade suppurative focus; that is, a subfebrile course, asthenia, anemia, myalgias and arthritis pains.

2. The abscess of the seminal vesicles was removed by what is believed to be a hitherto undescribed surgical procedure, transperitoneal seminal vesiculectomy.

3. Transperitoneal seminal vesiculectomy offers excellent surgical exposure of both seminal vesicles, permitting their complete enucleation under vision.

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16. Belfield, W. T.: Pus Tubes in the Male, M. Rec. **71**:731, 1907.

# CONGENITAL MALFORMATIONS OF THE HANDS

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CHICAGO

*(Concluded from page 53)*

## HYPOPLASIA AND APLASIA OF ELEMENTS OF WRIST AND HAND

Attention has already been drawn to hypoplasia of the distal elements of the hand, for example, the absence of any part of the digits from the smallest part of the distal phalanx or nail to the absence of the entire finger or thumb. It remains to discuss hypoplasia and aplasia of the intermediate elements, the carpus, metacarpus and phalanges. Again these various types of hypoplasias have been dignified by names and descriptions as clinical entities, such as brachydactylism, brachyphalangism, clinodactylism, etc. In this group, even more than in the groups that have been discussed, it is evident that these are not clinical entities but parts of a general picture of hypoplasia with associated disorientation. Every gradation from the simplest type of so-called clinodactylism to complete absence of one or many elements may be seen. In the same individual or in his family, the various so-called types may be found, as for instance, one hand may show clinodactylism and short metacarpals, while the other may show phalangeal aplasia or hyperplasia; a father may have short metacarpals, his children the same, or some other types of the process.

A study of these cases further emphasizes that the congenital anomalies have their origin in the germ plasm. The history of heredity is marked. Bilateral involvement of the hands with associated similar lesions of the feet are common, as are other congenital deformities. There are a very few lesions, such as the frequent absence of one of the phalanges in the little toe, especially in the Japanese race, or the origin of the biphalangeal thumb, that might lead one to speculate as to the phylogenetic history of variations. Practically all other reductions, however, find their only logical origin in some injury to the germ plasm. This injury is manifested in some degree of hypoplasia with associated disorientation. Thus we have hypoplasia and aplasia of phalanges and metacarpals associated with clinodactylism, symphalangism, hyperphalangism, syndactylism, polydactylism and even hypertrophy.

The hereditary nature is illustrated in many patients. In the group of 100 cases studied by ourselves, of which 78 were used for analysis, 37 gave a history of heredity. In 20 cases it was stated that it was not a family trait, and in 21 there was no statement given. Hall reports a family of 300 persons, 100 of whom had some type of brachydactylism and interphalangeal ankylosis. Breitenbecher traced a hereditary shortness of thumbs through five generations. Drinkwater investigated a family with brachydactylism going through seven generations with 25 persons living, in all of whom the twenty digits were short. Birkenfeld found 332 relatives affected in 103 cases.

Hypoplasia of the carpus is usually seen with hypoplasia of the radial element (absence of radius and the thumb) or of the ulnar element (absence of ulna). Its simplest form finds examples in the cases of Eaves and Campiche, Connelley and Court, Botreau-Roussel, in which, in addition to absence of the scaphoid and semilunar with adjacent hypoplastic carpal bones, the styloid process of the radius was absent—manifestly a small destructive lesion of the radial element. Hoffman's case was a similar radial lesion without styloid involvement affecting the scaphoid, semilunar, multangulum minus and minus. Muller's case was similar with an hypoplastic thumb. No case of isolated ulnar hypoplasia of carpal bones alone has been found.

The radial lesion presents clinically some luxation and radial deviation of the hand. The disability is not great, and no treatment is indicated except possibly splinting of the growing hand to encourage growth in as nearly normal relations as possible.

Metacarpal hypoplasia may be seen alone or in conjunction with phalangeal change. In 42 cases of brachydactylism with metacarpal involvement, 31 had involvement of metacarpals alone and 11 had an associated shortening or absence of the phalanges (fig. 25).

In addition to shortening, the metacarpal often shows an atypical growth and attachment of the epiphysis. Infrequently an epiphysis may be found at both ends. The shadow on roentgen examination is often less dense than normal. There may be variations in the form of the diaphysis, and almost any grouping, unilateral or bilateral, may be present. In our studied group, 29 cases were bilateral and 13 unilateral. In the 29 bilateral cases, the same metacarpals were involved in both hands in 27 and in the 2 other cases the same metacarpals with an extra one were involved in one hand. In 2, all ten digits were involved and in 1 the second, third, fourth and fifth digits; in 2, the first digit was involved, and the remainder, largely the fourth digit or some combination of the fourth with the third and fifth digits. In the 13 unilateral cases, 1 showed involvement of all five digits and 7 showed involvement of only one digit.



The relative frequency of digital involvement in all cases is shown by the fact that in the 42 cases the first digit was involved in 8 cases, the second digit in 5 cases, the third in 15 cases, the fourth in 28 cases and the fifth in 17 cases.

The phalangeal aplasia and hypoplasias vary from clinodactylism with a simple skin and subcutaneous contracture or the more typical form of a distorted joint and contracted capsule producing lateral, palmar or dorsal deviation, through latent hyperphalangism, manifest hyperphalangism, symphalangism to hypoplasia and aplasia of phalanges.

Clinodactylism finds its origin in most instances in disorientation of the epiphysis producing improper alinement of the joint surfaces with

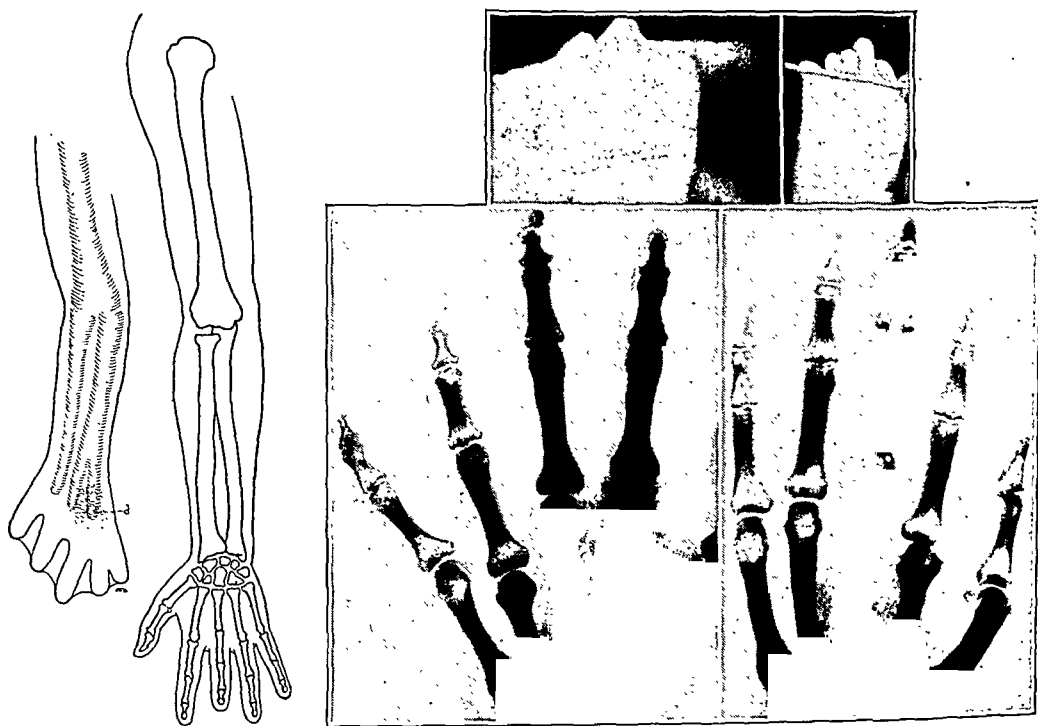


Fig. 25.—Brachyphalangism and brachydactylism. The photographs show the fingers with brachyphalangism in case 27. The roentgenograms show two types of brachydactylism from metacarpal hypoplasia (cases 46 and 47). The schematic drawing shows the manner of origin. The dots represent disorientation of the embryonal tissue.

corresponding change in the capsule. It is most often seen in the little finger and not infrequently in the distal joints, but may involve any finger or any joint. It may be seen alone or in conjunction with other lesions. Some authors would restrict the term clinodactylism to contractures of the little finger involving particularly the distal phalanges and would introduce the term camptodactylism to describe somewhat similar lesions of other joints and fingers particularly when associated with stiffness of the joints. To our minds, however, these variations are differences of

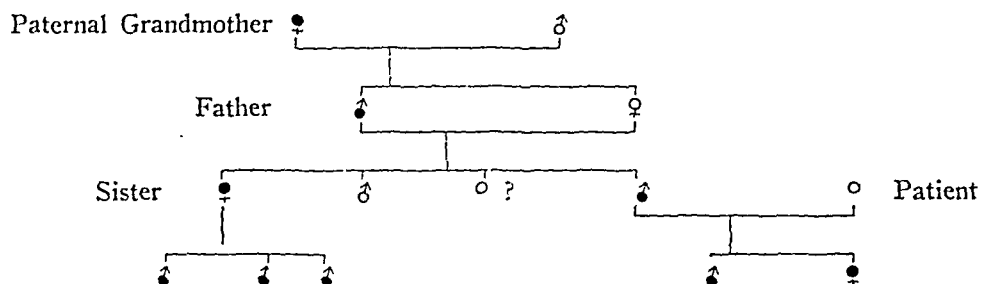
degree and location only; therefore, no such distinction should be made. Illustrating these variations the histories and photographs of some of the patients presenting themselves in our clinic are presented.

CASE 58.—*Bilateral clinodactylism of the little finger.*

The patient presented a bilateral radial deviation of the terminal phalanges of both little fingers. The middle phalanges were short and distorted, but the movements at the joints were normal. The right second toe was longer than the great toe.

The patient's two children, a boy and girl, exhibited the same deformity; in the boy the deformity was more marked in the left hand than in the right.

The family history showed the same lesion running through several generations as illustrated in the accompanying diagram, the dark circles showing the affected members.



The following case history illustrates a similar lesion. It will be noted that the mother and brother present typical simple bilateral clinodactylism. The patient presents a similar lesion in the left hand; the right, however, shows associated disorientation of the middle and ring fingers in addition to the clinodactylism of the little finger, an added proof that the lesion although hereditary shows variations dependent on the degree of germ plasm injury and that clinodactylism is not a distinct clinical entity but rather a stage in germ plasm injury that may vary from generation to generation and in different individuals of the same generation.

CASE 57.—*Bilateral clinodactylism of the little fingers and associated disorientation of the right ring and middle fingers.*

The patient presented a radial and palmar deviation of the distal phalanx of the little finger of the left hand. In the right hand a similar lesion was present in the little finger. Between the ring and middle fingers was a short web, and there was marked disorientation of the two distal phalanges of both fingers. There was no limitation of motion in the little fingers, but there was marked limitation in the distal phalanges of the middle and ring fingers of the right hand.

The mother and brother showed similar bilateral clinodactylism of the little fingers.

It will be seen by examining the photographs presented herewith of other patients with more extensive destruction that clinodactylism in varying degrees is a not uncommon accompaniment. It may be seen with any of the congenital lesions of the hand. For example, Mosenthal and

Scharff report a family showing hyperphalangism of the second digit, brachymesophalangism of the third digit, clinodactylism of the fifth digit in varying degrees or absent in various members. Pol noted clinodactylism of the fifth digit and hyperphalangism of the second and third digits in six different families.

The treatment in the simple cases with slight bone involvement is very satisfactory if instituted early in life. It consists in applying aluminum splints worn for several months to favor the stretching of contracted ligaments and growth in proper alinement. At times it may be necessary to apply tension to overcome the contracture. In the simple form, however, there is little or no disability attending the lesion. Trousseau suffered from this deformity.

Hypoplasia or aplasia of the phalanges (brachyphalangism) is seen in all five digits (see fig. 25). Almost any combination of phalangeal reduction may be seen. In the analysis of both hands in the 78 patients

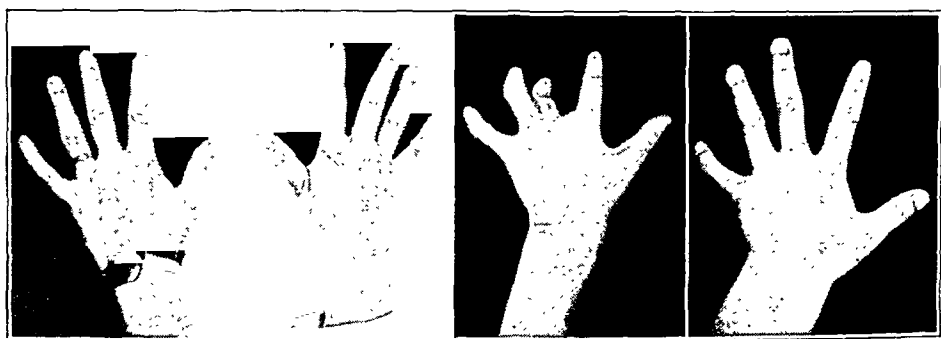


Fig. 26.—Clinodactylism in case 58. The adult hands, those of the mother, show bilateral clinodactylism; the child's hands, the son's, show bilateral clinodactylism of the fifth digit and disorientation of the third and fifth digits.

with brachydactylism already referred to, we found the middle phalanx hypoplastic in 17 and absent in 18, a total of 35; the distal phalanx was hypoplastic in 11 and the proximal phalanx hypoplastic in 13. It is seen that, excluding distal aplasia, simple phalangeal absence is nearly always of the middle phalanx. Counting all digits on both hands the thumb was involved in 6, the index finger in 43, the middle finger in 37, the ring finger in 28 and the little finger in 41. In other words, there was not much difference in the percentage of fingers involved; the thumb, however, commonly escaped. This must not be interpreted as meaning that the thumb is infrequently involved, since Hilgenreiner has collected reports of 107 instances of three-jointed thumbs. In one patient all the phalanges of the fingers in one hand were short; in another the distal and middle phalanges of the second and third digits were affected; in two patients the middle phalanx was absent in all five digits of one hand; in two others, they were absent in the four fingers

of one hand, and in one patient with well formed fingers the distal phalanges were absent in all five digits of one hand. Esau and Pfitzner have presented in figure 27 the various groupings they found in a study of the literature. As previously noted, we have observed additional types.

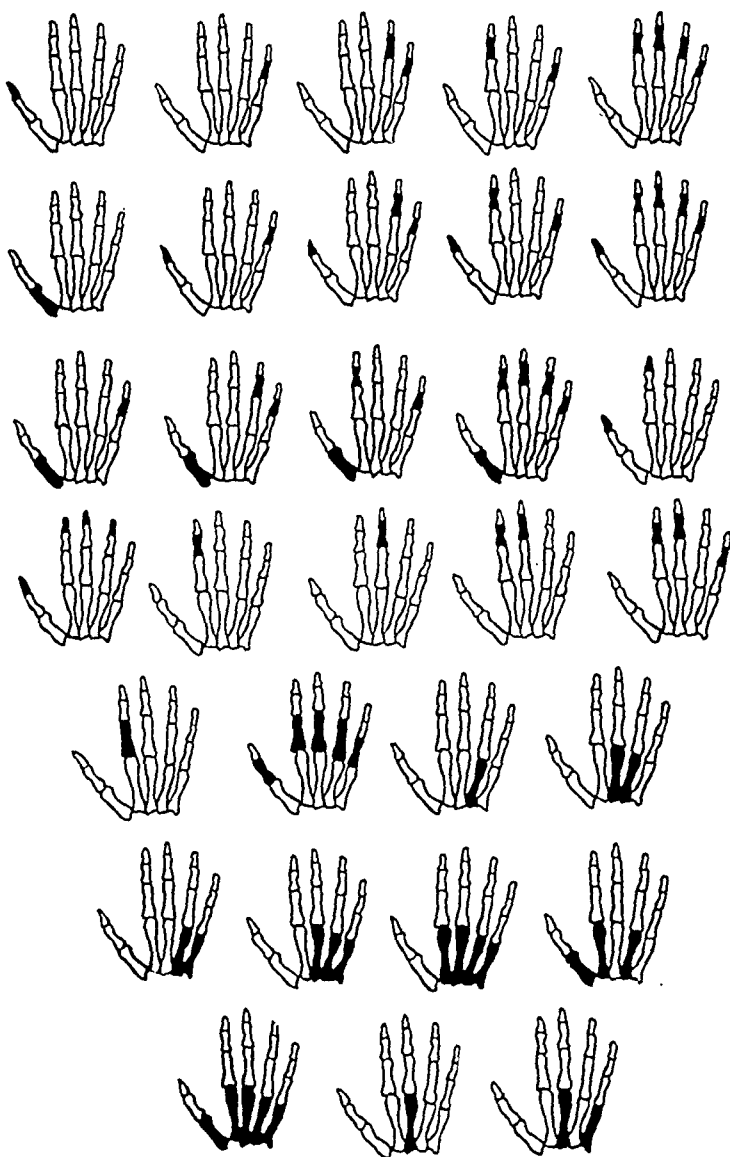


Fig. 27.—Types of brachydactyly reported by Esau and Pfitzner.

Hypoplasia, aplasia, latent and manifest pseudohyperphalangism and symphalangism probably generally have their origin in disorientation of the epiphyses. In hypoplasia, through disorientation and possibly premature ossification, the epiphysis ceases growth or grows in an atypical manner, while the diaphysis continues to grow, ending in broad distorted bones. Associated with this one may find biterminal epiphyses.

As has been said, any phalanx may be involved; it is more common, however, to see shortening of the middle phalanx.

The next stage is that in which one sees in addition to the middle phalanx a disorientation of the epiphysis of the proximal phalanx with overgrowth of the radial side so that a protuberance develops, so-called latent hyperphalangism. If this growth continues, there is a separation of this protuberance to become an atypical proximal phalanx in a four

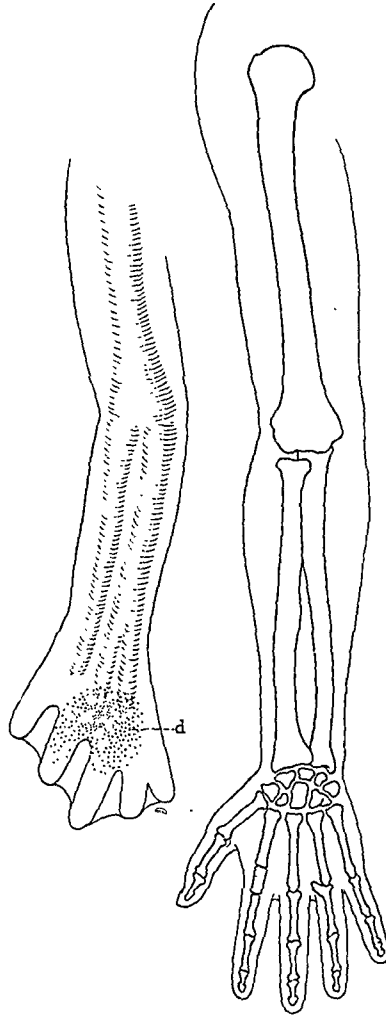


Fig. 28.—Schematic drawing illustrating origin of manifest (second digit) and latent (fourth digit) hyperphalangism from disorientation of embryonal tissue. (See case 16, fig. 42; case 32, fig. 18; case 44, fig. 8.) The fifth digit represents symphalangism from the same origin. (See case 40.)

phalangeal digit, manifest hyperphalangism (fig. 28). In some instances one sees the shortened middle phalanx united to the distal phalanx without evidence of a joint, assimilation hypophalangism. This may occur with the reduplication of the proximal phalanx so that in spite of the extra phalanx added proximally there are still three phalanges. Variations in these processes may occur, as, for instance, Duken reported

a unilateral hypoplasia of the middle phalanx in all four fingers with symphalangism between the middle and proximal phalanges of the index, middle and ring fingers and between the middle and distal phalanx of the little finger. In addition to the proof we have of this origin of hyperphalangism through observation of successive stages in various patients, we find supporting evidence in the fact that the flexor sublimis attaches to segment three and the profundus to segment four, while the extensor digitorum communis attaches to segments three and four. Therefore, we believe that segment one has its origin from the proximal epiphysis; segment two is the primary proximal phalanx; segment three is a much reduced middle phalanx and segment four is an original distal phalanx. Aplasia of the middle phalanx may be seen with or without reduplication of the proximal phalanx ending in biphalaengeal fingers or spurious triphalangism.

These various types of phalangeal disorientation may be seen in the same individual or in succeeding generations.

Vidal reported the case of a patient with short middle phalanges in all four fingers of one hand and stated that the condition ran through five generations with either latent hyperphalangism of the second digit alone, or latent hyperphalangism of the second digit with manifest hyperphalangism of the third digit or manifest hyperphalangism of both second and third digits. In the five generations there were 10 cases of hyperphalangism, 20 of clinodactylism and many instances of other congenital deformities such as syndactylism and hypoplasias of various types. Geelvink studied three members of the same family. One had a short metacarpal of the thumb with a short middle phalanx of all the fingers in one hand, short middle phalanges of the index and middle finger of the other hand and latent hyperphalangism of the index finger in both hands. The brother and son of the first had practically similar lesions with manifest hyperphalangism of the middle fingers and latent hyperphalangism of the index fingers. Klasner, Joachimsthal and many others reported some similar observations.

The hereditary nature of the general type is evidenced by numerous examples.

Some consideration should be given to the question of triphalangism in the thumb. Here, if any place, one may assume a phylogenetic origin. The controversy has been almost acrimonious without arriving at a decision. Some think the biphalaengeal thumb arises from absorption of a phalanx as a rule, while in the fingers it is seen only occasionally. Others think the metacarpal is really a phalanx with an absorption of the metacarpal. Joachimsthal believes that at times the triphalaengeal thumb arises as a duplication of the index finger with an absence of the true thumb. Others assume the triphalaengeal thumb to have its origin in a process similar to that described for the four phalangeal fingers.

This latter origin seems to us more probable. We base this on the presence of associated evidences of disorientation. Bateson reported a bilateral triphalangeal thumb with accessory hypoplastic biphalangeal rudiment; Spronk, a unilateral reduplication of a triphalangeal thumb; Windle, Farge and Guernonprez, right triphalangism and syndactylism between the index finger and the thumb and a left similar deformity with an accessory rudiment of the thumb.

In addition to the assimilation hypophalangism already discussed, simpler forms of symphalangism are seen, described, unjustly we think, as true symphalangism, for instance, a simple union of two phalanges without other deformities. These simpler forms are, to our minds, an expression of the same disorientation process differing only in that it affects the joints and is of a milder degree, although it may be found as an accompaniment of other congenital deformities of the hand. It may involve single or many joints. Pagenstecher reported symphalangism of both joints at the little finger, the distal joint of the middle finger in the left hand, with brachydactylism in the right hand and symphalangism of both joints of index finger and the distal joint of the ring finger. One of our polydactylous and one of our hypoplastic cases showed symphalangism.

In addition to the intimate association of the various lesions in the hand itself that have already been discussed, such as syndactylism, hypoplasia, symphalangism, polydactylism, brachydactylism, etc., other distant congenital deformities are seen not infrequently. Pol collected 38 cases of brachydactylism with associated syndactylism, in 20 of which there was some disorientation of the structures of the upper part of the arm including 19 with defects of the pectoral muscles. Analogous deformities are frequently seen in the feet.

*Fusion of Hand and Arm Elements (Symphalangism, Carpal Fusion, Radio-Ulnar Synostosis).*—In addition to the symphalangism already discussed, there is fusion of digits, metacarpals, carpals and arm elements. It would seem that this fusion is an expression of a mild disorientation of tissue which originated in the germ plasm and is expressed by a lack of proper differentiation of the elements.

In the fingers there is every grade from simple webbing to partial or complete fusion of all the finger elements. This will be discussed when syndactylism is considered. There is lack of differentiation also of the metacarpals, the degree varying from complete fusion to the separation of the metacarpals except for a small attachment. More commonly such nonseparation is seen at the proximal end.

Fusion of the carpals may appear as an isolated phenomenon or in association with that of other bones. Other congenital lesions may be present. Many groupings of fused carpals with the absence of other

carpal bones are reported, as, for instance, fusion, unilateral or bilateral, of the semilunar and scaphoid with or without distortion of adjacent bones; fusion of the semilunar with unciform and cuneiform and of the os magnum with the trapezoid; fusion of the semilunar with the os magnus and unciform, scaphoid atypical in form; fusion of trapezium with the first metacarpal, and of the trapezoid with the second metacarpal.

**Radio-Ulnar Synostosis:** Because the picture is more or less uniform, congenital radio-ulnar synostosis has been classed as a clinical entity. The disorientation finds its chief expression in the failure of separation of the ulna and radius at their proximal ends. The union commonly extends over 3 to 5 cm., although it may be more or less. There are two types, first, that in which the union occurs in the normal position and second, that in which the head of the radius is dislocated anteriorly and exceptionally posteriorly. The surrounding structures may be normal with the exception of the shortening and atrophy of the muscles having to do with supination, or more or less disorientation of the surrounding structures may be present. The embryonic radius lies in pronation, the ordinary position of the radius in these cases. It is frequently thickened and bent outward, thus producing a wide interosseous space. However, Boskoschny reported a case with a normal form of radius and a thickened ulna, and Wilkie and Feidt reported a case with thickening of the distal end of the radius. The supinator muscles are deficient; Dawson reported a case in which the supinator brevis was absent. The pronators are shortened, and the axis of function of the other muscles is changed.

In the second type with greater disorientation, the head of the radius may be partially absent and the radius itself is commonly dislocated anteriorly with an atypically placed articular surface on the lower end of the humerus; the orbicular ligament may be aplastic, and not uncommonly the lesion is associated with other deformities of the radial element as would be expected, e. g., radial syndactylism (Reise), polydactylism of the thumb (Schmid), absence of both thumbs (Joachimsthal), right forearm short with a small hand and hyperflexion at elbow (Blumenthal), and short humeri (Boorstein). Distant associated congenital anomalies are also reported, e. g., abnormal knee joints in a father and son (Roskoschny), club feet and, a not infrequent finding, mental deficiency.

The hereditary nature is well established. Abbott recorded 7 instances out of 40 persons in five generations, and Beuchard, Blumenthal, Feidt, Pförringer, Ombredanné and von Sury have made similar observations.

Greig collected reports of 84 cases. In this group there were 47 males and 32 females; the sex of the others was not mentioned. The



condition was bilateral in 59 cases, and of the remainder, left-sided in 16 and right-sided in 9 persons.

These observations prove this lesion also to have its origin in the germ plasm, and we may assume that the varying pictures are but an expression of the degree of germ plasm injury, so that while for the sake of discussion we may speak of two types, yet in reality no such clear distinction exists.

Synostosis of the distal ends of the ulna and radius is uncommon, although the case reported by Appraille proves that the deformity may occur.

There may be little interference with function, as is shown in our case herewith presented (fig. 29 A). The patient, a physician, complained of little or no disability. There may, however, be considerable impairment of function. Supination is carried out very largely through the action of the arm and shoulder. This action is naturally inadequate and at times is a severe handicap, especially in the higher degree of disorientation.

In the more disabling lesions operative treatment may be indicated. Kummel and Rais divided the synostosis in their cases. In Rais' case at least no improvement of function occurred. After division of the bony union, Schilling interposed the extensor carpi radialis and secured such improvement that there was 78 degrees of rotation in two months. Aitken used the anconeus. Morestin and Stretton, after separating the ulna and radius, resected the head of the radius and secured marked improvement. Dawson operated on his patient five times, dividing the bridge, freeing the head of the ulna and dividing the interosseous ligament, but secured no benefit until he excised the head of the radius. Sever obtained the same result by the much simpler procedure of osteotomy on the shaft of the radius distal to the synostosis. This operation is simple and yet as certain of good results as more complicated procedures; therefore, we quote his description of the procedure. "An incision  $1\frac{1}{2}$  inches long was made on the outer side of each forearm about two inches below the elbow joint. About  $\frac{1}{2}$  inch of each radius was resected. The arms were put up in plaster casts fully supinated and kept so for six weeks." While Sever's case did not require division of contracting fascial bands, interosseous ligament or shortened fibrosed muscles, division may be necessary in some instances. It will generally be advisable to insert adjacent connective tissue or muscle between the ends of the resected bone to prevent bony union. The procedure should always be followed by intensive and prolonged physical therapy designed to develop the atrophic muscles, to maintain mobility and to educate the child in the use of the hand.

## SYNDACTYLISM

In the consideration of syndactylism, too often the clinical pictures of the simpler forms are presented as the typical picture of the malformation and no consideration is given to its appearance in association with the hypoplasias and aplasias. On an analysis of these simpler

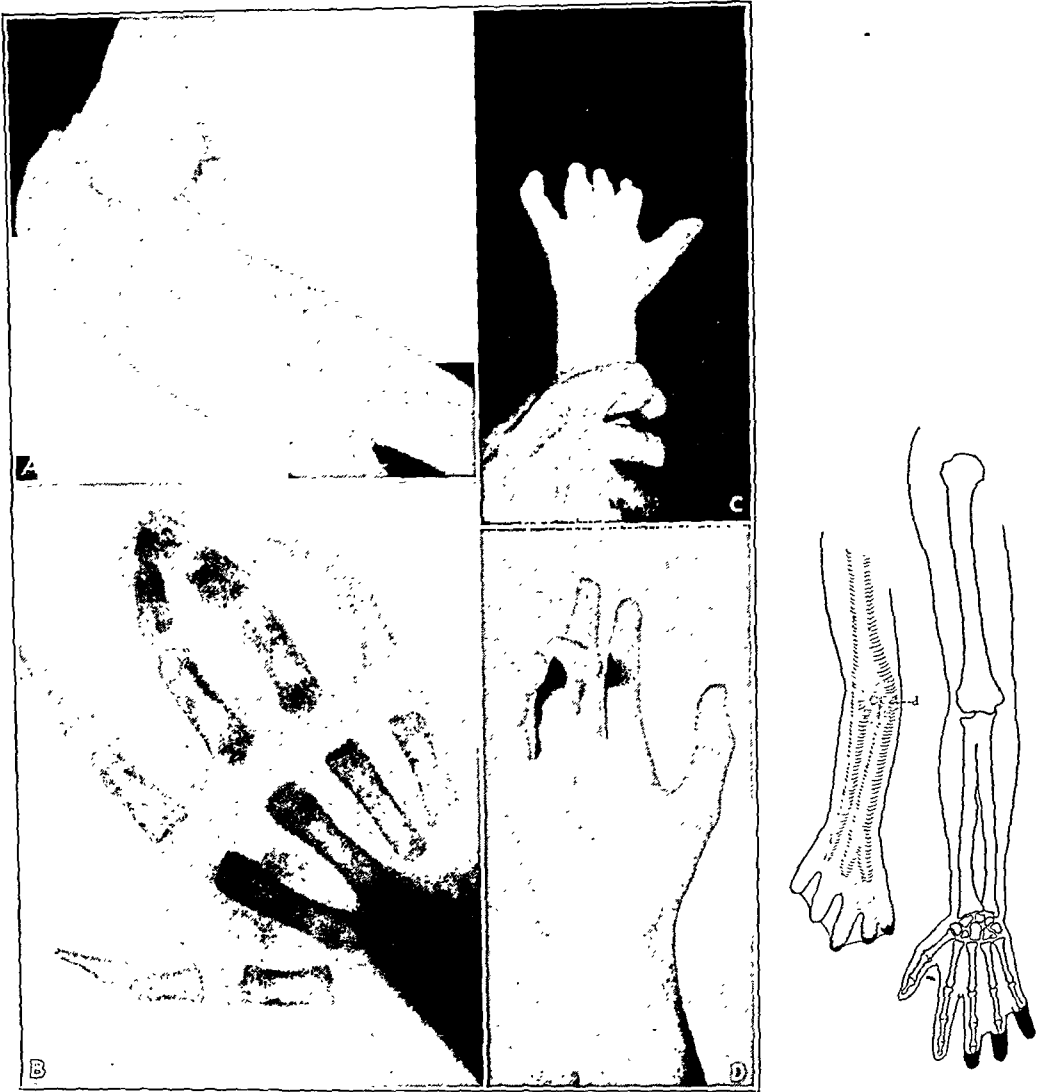


Fig. 29.—*A*, radio-ulnar synostosis in case 53. *B*, ulnar syndactylism with clinodactylism and beginning polydactylism of distal phalanx (fourth) in case 17. *C*, aplasia of the second, third and fourth digits with syndactylism in case 24. *D*, syndactylism and disorientation of the third and fourth digits in case 12. The schematic drawing illustrates the origin of radio-ulnar synostosis and ulnar aplasia with syndactylism.

forms, deductions as to etiology, pathology and clinical pictures have been made. A study of the problem, however, discloses that syndactylism, wherever it appears, is the result of the same process of disorientation of tissue growth expressed only in a difference of degree.

When one considers these various clinical pictures it is evident that any assumption that syndactylism arises as a reversion to the type of our amphibian ancestors has no reasonable foundation and that the only reasonable hypothesis is that it is an expression of disorientation of tissue growth arising probably through germinal origin. This has already been considered in the general discussion of the origin of congenital malformations. The simpler forms, skin and connective tissue syndactylism and syndactylism with polydactylism without hypoplasia, are an expression of disorientation of growth not sufficiently great to cause destruction of tissue. The complicated forms, syndactylism with hypoplasia and aplasia, follow as a result of disorientation of tissue growth around an area of necrosis, similar to the picture seen in abscess formation in adult tissue where around the central necrosis appears round cell infiltration followed by scar tissue growth binding all structures together into an atypical mass of muscular, vascular and nerve tissue.

For the sake of clearness it may be advisable to divide our cases into these two types. It will be seen from an analysis of our personal cases that while there is every gradation of tissue change from the simplest to the most complicated form, yet a simple grouping of those appearing without and those with aplasia illustrates two rather dissimilar clinical pictures. It will also illustrate the predilection of syndactylism for the embryologic ulnar and radial groups predicated previously in the general discussion of etiology.

In the 60 cases of congenital malformations used for study, 34 showed some degree of syndactylism. If these are divided into four degrees, the first two simple and the last two complicated with aplasia, these degrees would be as follows: first degree, skin and connective tissue only; second degree, soft tissue combined with bone fusion or disorientation, i. e., fusion or polydactylism; third degree, peripheral aplasia with syndactylism; fourth degree, central aplasia with syndactylism. A study of these presents the following statistics:

		Bilateral	Left	Right	Total Hands
1st degree .....	13	6	12	7	19
2nd degree .....	7	4	6	5	11
3rd degree .....	6	2	4	4	8
4th degree .....	8	3	7	4	11
		—	—	—	—
		15	29	20	49

An analysis of all hands (49) as to digits involved follows:

	I	II	III	IV	V
1st degree—Left ..	1	3	12	11	1
Right..	1	1	7	6	1
	—	—	—	—	—
	2	4	19	17	2

[illegible]

The discrepancy in figures in the complicated forms is due to the complete aplasia of elements in certain hands.

When we analyze these figures we see that in the simple forms in practically all instances the lesion is found involving the ulnar or the ulnar and medial elements alone, which is what one would expect when it is remembered that the thumb arises separately from the radial element. On the other hand, where there was serious aplasia, which must occur earlier in embryologic formation before separation of the buds, the radial element (thumb) is frequently found combining with the medial element (index finger) or all the digital elements may be involved.

An analysis of our cases in relation to the four arbitrary degrees mentioned discloses the following:

*First Degree.*—Syndactylism of soft parts only, 17 hands. The syndactylism was between the third and fourth digits exclusively in 10 cases; the second and third digits, 1 case; the second, third and fourth digits, 1 case, and the third, fourth and fifth digits, 1 case.

*Second Degree.*—Syndactylism with bone involvement or polydactylism, 13 hands. The syndactylism was between the third and fourth digits exclusively in 10 cases; the fourth and fifth digits, 1 case; the first, second and third digits, 1 case, and the first and second, third and fourth digits, 1 case. Eleven of these hands showed polydactylism, 2 being of the fifth digit, the others of the third or fourth (see figs. 42 and 43).

*Third Degree.*—(a) Distal peripheral aplasia with syndactylism. Here one would expect a diffuse superficial lesion more marked at the periphery due to the superficial blistering and superficial destruction with proximal simple syndactylism (see figs. 2, 9, 24, 29 and 42). An examination of this group discloses five hands presenting the clinical picture of close bony fusion of distal phalanges, at times with beginning polydactylism of the distal phalanx (see fig. 29 B) with soft tissue syndactylism proximally, generally involving the four fingers and sometimes the thumb also.

(b) Ulnar or radial peripheral aplasia and syndactylism. These forms grade into the peripheral distal type. They are associated with ulnar or radial hypoplasia of greater or lesser degree and are characterized by distal aplasia and proximal syndactylism of the part involved (see figs. 11 and 12).

*Fourth Degree.*—Extensive central aplasia with lateral syndactylism and proximal syndactylism, if any rudiments of central digits are present. Here, owing to the severity and extent of the lesion, the radial element (thumb) is frequently bound to median element (index finger) and the ulnar elements remaining are bound together (see fig. 14). If rudiments of the central digits remain, the digits are frequently all combined together sometimes in bizarre forms (see figs. 14 and 16).

It must be clearly understood that these degrees are not described as separate clinical forms since each degree grades into the next. They are separately described only with the purpose of presenting a composite picture of syndactylism and explaining its genesis. Moreover, I am aware that an analysis of a larger group would certainly present a quite different summary of digits and parts involved, but that the general deductions will be found true is believed. The presentation does give one a conception of the genesis of syndactylism and an explanation of the associated lesions: polydactylism, symphalangism, bone fusion, other forms of disorientation and aplasia.

In passing, it is interesting again to draw attention to Bagg's statistics of experimental inbred foot defects in 413 animals, 300 of which had club feet with syndactylism and 9 syndactylism alone. The frequency in man of associated foot defects and occasional presence of other congenital malformations should also be mentioned (e. g., case 29, foot defect, hypospadias, closure of Steno's duct; case 34, defects of femur and fibulae).

The hereditary tendency, particularly in the simpler forms, is well marked. For example, one patient (case 15) had two sisters, one nephew and a cousin; another (case 18) had a maternal father and grandfather, an uncle and a child with similar lesions. In the more severe forms with aplasia the hereditary history was not so marked.

The union of the digits may be of any degree, simple skin and connective tissue with a wide separation or closely bound together even to complete bony union. The interdigital blood vessels and nerves may be separated or fused throughout any part of their length. The tendon sheaths may be separate or partly or completely fused (case 14). The tendons may be separate, lie in a common sheath or be fused (case 32). The bones may be partially fused, especially the distal phalanx (case 17) or throughout their length. The nails may be completely fused. Disorientation of joints and soft tissue may give rise to fixation or to contracted and distorted digits.

In polydactylism the extra digit may be of any size and have any degree of fusion with the normal digit and frequently shows considerable distortion in growth. Aplasia has already been discussed in a previous section where also will be found a consideration of disorientation of the bones both as to shape and position.

#### TREATMENT

For over a century the treatment for syndactylism has followed the changing conceptions of the principles of surgery, first the crushing and cutting of the webs, then the production of a scar-lined canal at the web followed by the cutting of the web, later the introduction of epithelial lined canals by pedicled flaps and various types of flaps from the fingers to cover the defects on the sides following the cutting of the web. Subsequently, the introduction of Thiersch grafts to supplement these various procedures improved the results, although in many instances they left much to be desired. With the introduction of the full thickness free skin graft, our conception of the proper care of these patients was completely revolutionized. Instead of the skin graft being simply a supplement to the older methods, we now conceive it to be the principal factor in treatment and the earlier procedures to be subsidiary or to be used only in the simplest forms. The reasons for this are manifest to any one who has had experience with them. On paper, the operative procedures as sketched appeared to be ideal, but when applied in practice, except in the simplest cases with a wide web, they were found to be inadequate and were followed by contracture of the fingers and partial return of the web. No matter which type of operative procedure had been chosen for the individual case, when the fingers were separated the available skin was almost always found to be inadequate, and a defect would be left, or, as the surgeon would suture the flaps with tension, the skin would either slough or, if it healed, would be bound so tightly as to interfere with function. If the defect was covered by a Thiersch graft over scanty subcutaneous tissue, mobility was impaired. The extensive scar tissue formation

following the more complicated procedures or the subsequent contraction of the line of scar in the simpler procedures gave unfortunate sequelae. Unless the commissure was reestablished with normal skin without a scar across it, the result was not ideal.

With a free full thickness skin transplant these disabilities can be avoided and a nonbinding, mobile covering of the defect be secured with a far better result and greater promise of permanency. In the simplest cases and as a supplement to skin grafting, the older procedures may be used to advantage. No surgeon, however, should approach any case without being prepared to do a skin graft, since the defect is always greater than is anticipated. On the other hand, since older methods do have advantages in some instances, a familiarity with them is necessary, and therefore a brief description of the more common procedures is given.

The earliest procedures aimed only at severance of a wide web and consisted of some form of pressure applied between the fingers, such as a cutting ligature, forceps, glass prisms, etc. (Maisonneuve, Verneuil, Giralde, Dupuytren, Fabric and others). Such a procedure could be applicable only to the simplest cases and is based on improper surgical principles, since subsequent contraction of the scar with return of the syndactylism is likely to occur. Simple incision with suture has the same objection to its use.

The next stage in the development of the operative procedures was the introduction by Rudtorffer (1801) of a tunnel through the base of the web produced by drawing through a lead thread which was permitted to remain until cicatrization took place. Later, the remainder of the web was severed by clamps. Others used silver wire, India rubber cords and glass tubes. After forming the cicatrized canal, Velpeau cut and sutured the web. The same objection can be made to these methods as to the earlier procedures.

A new principle was introduced when Zeller (1810) proposed to make an inverted V-shaped flap of skin on the dorsum of the web with its base at the metacarpophalangeal joint. The remainder of the web was cut in the midline and sutured, the tip of the inverted V skin flap being drawn across the commissure and the tip sutured to the palm. Agnew later suggested practically the same procedure. The production of an epithelial covered commissure was a real advance. As the tip of the flap was liable to slough, Dieffenbach made the next advance in his suggestion that the flap should be quadrilateral rather than triangular (fig. 30).

Morel-Lavalle and Morton now suggested that instead of one flap two should be made, one palmar and one dorsal. Morel-Lavalle's suggestion was for two triangular flaps, the tip of the palmar one to be

brought through to the dorsum and the dorsal to the palmar surface. The tips were sutured to the respective surfaces and the flaps side-to-side. The remainder of the web was cut and sutured over the respective fingers.

Félizet (1892) introduced a new principle. Palmar and dorsal quadrilateral flaps were made at the base of the web. The palmar flap had its base proximal in the palm, the dorsal flap its base distal on the web with the free end raised proximal from the base of the web. A wide opening was then made through the connective tissue holding together the bases of the proximal phalanges, and the flaps

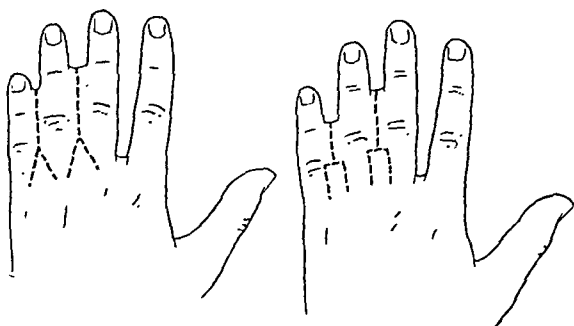


Fig. 30.—Zeller-Dieffenbach's operative procedure for syndactylism.

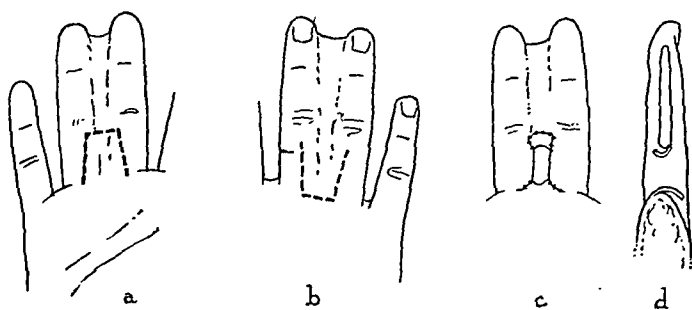


Fig. 31.—Félizet's operative procedure for syndactylism.

were drawn through. The palmar flap was sutured to the cut edge of the skin over the metacarpophalangeal joint, and the dorsal flap was sutured to the edge of the palmar surface of the web. A canal was thus formed which was lined distally by the dorsal flap and proximally by the palmar flap. Later the remainder of the web was severed and the edges were sutured (fig. 31).

Another step in the operative procedure suggested by Didot (1850), followed by Diday in the same year and later by Nélaton (1884), has been widely used by surgeons. No operation could appear more ideal when presented in schematic form and yet give rise to more unsatisfactory results when applied to the average case than this procedure. In certain instances, however, the principle is of value. The attempt



to apply it universally is disastrous, since the flaps are seldom found to be adequate, and moreover the commissure is not well covered by skin.

The Didot operation consists in making quadrilateral flaps with the base extending the length of the artificial web. A dorsal flap is made by making a longitudinal incision on the dorsum of one of the involved fingers (*A*) the length of the web with two transverse incisions at the end of the longitudinal incision. The transverse incisions extend to the middle of the dorsum of the other affected finger (*B*). This flap is raised from the subcutaneous tissue, being still attached throughout its length on finger *B*. An incision similar in form is made on the palmar surface except that the flap is reversed, the base remaining attached to finger *A*. The interdigital connective tissue is cut and the flaps wrapped around the respective fingers, one being sutured on the dorsal and the other on the palmar surface of the respective fingers, *A* and *B* (fig. 32).

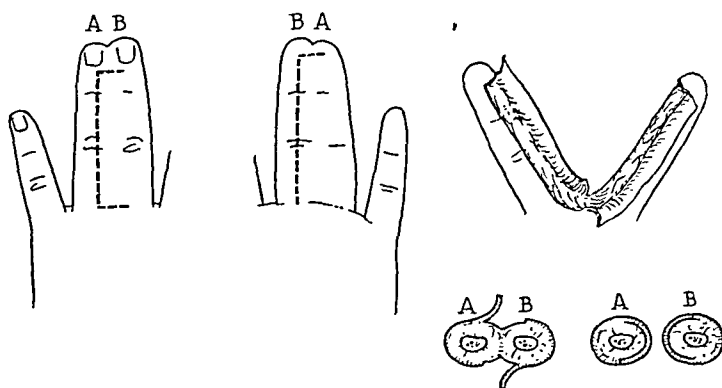


Fig. 32.—Didot's operative procedure for syndactylism.

Tubby (1912) combined Félizet's and Didot's procedures. After a canal was made through the base after the method of Félizet, as previously described, a glass rod was inserted and held in place by supports extending downward from a metal cuff around the wrist. After healing had taken place, the respective fingers were covered with skin by Didot's method, the glass rod still being used to retain the commissure in a proper position.

A new feature was added by the procedures of Faniel (1911) and Rudulesco (1923). They sought to avoid some of the disadvantages of the Didot operation by making the flaps in a different form. Faniel's operation consists in making Z-shaped incisions on the dorsal and palmar surfaces across the web and the involved fingers. If digits *A* and *B* are involved, the dorsal incision begins at the middle of the dorsum of digit *A* at the distal level of the congenital web and is carried transversely across to the middle of digit *B*; from here it passes obliquely downward to the middle of the metacarpophalangeal joint of *A*, then

obliquely upward and transversely to the middle of the dorsum of the base of the proximal phalanx of digit *B*, thus producing two triangular flaps with the pedicles attached to the dorsum of the two digits, respectively, the upper flap to digit *A* and the lower to digit *B*. On the palmar surface a similar incision is made, but reversed so that on the flexor surface the upper flap is attached to digit *B* and the lower to digit *A*. After the connective tissue web is removed, the dorsal and palmar flaps of digit *A* are wrapped around that finger and digit *B* is covered in a similar manner (see fig. 33).

Rudulesco, in an effort to avoid the sloughing of the apexes of the triangles noted following Faniel's operation, suggested making the reversed incisions in the form of a question mark. Here the dorsal incision begins at the distal end of the web at the junction of digit *A* with the web. The incision is carried proximally half way up the

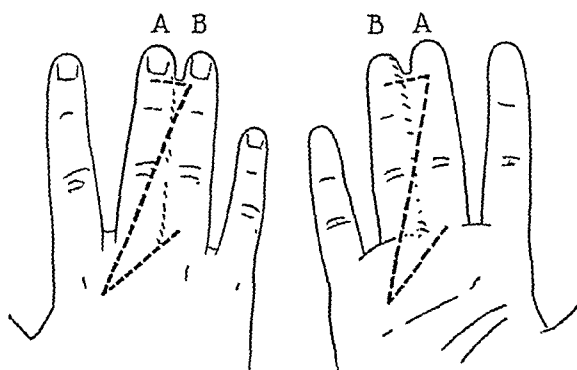


Fig. 33.—Faniel's operative procedure for syndactylism.

finger, then crosses obliquely across to the dorsum of digit *B* and proximally in a curved line down to the metacarpophalangeal joint, then curving across to the base of digit *A* and somewhat distalward. A reversed incision of similar nature is made on the palmar surface not extending so far down in the palm, however. Thus in the distal part the operation is similar to the Didot procedure, while proximally there are two rounded flaps of skin, one palmar and one dorsal. The palmar flap is brought about the base of the finger to which it is attached and the dorsal about the other, and the edges are sutured together in commissure. If necessary, Thiersch grafts cover any defects (fig. 34).

Villechaise and Jean (1927) combined the Zeller-Dieffenbach-Didot operations, making a palmar quadrilateral flap extending well to the end of the web with its base proximal. On the dorsum they used two quadrilateral flaps by making a longitudinal incision the length of the web through its middle, then two transverse incisions at the ends extending to the middle of the dorsum of each involved finger. These flaps then were raised, their bases being attached to the respective fingers

longitudinally the length of the web. The palmar flap was brought across the commissure and attached to the edge of the dorsal skin, and the longitudinal flaps were wrapped about the respective fingers (fig. 35). If the fingers were closely attached with little web, they suggested taking a long pedunculated flap from the dorsum of the hand with its base at the metacarpophalangeal joint and its apex proximal and lateral. This was swung to cover the defect on the side of one finger. Others have suggested similar procedures. Should such pedicled grafts be used, they should be tubed, but where such an extensive plastic operation is advisable, surely free full thickness grafts are preferable.

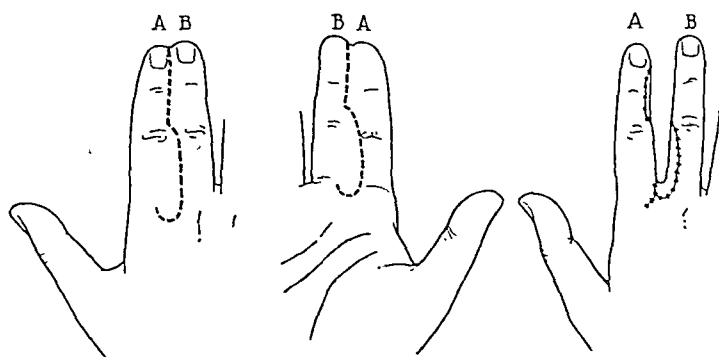


Fig. 34.—Rudulesco's operative procedure for syndactyly.

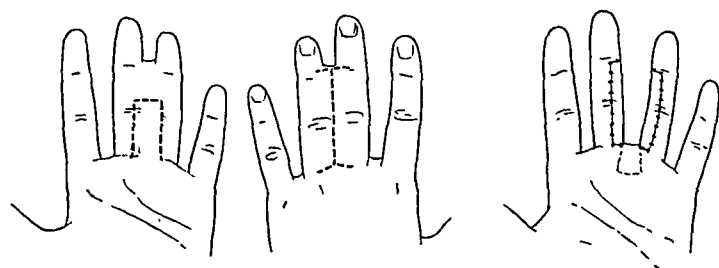


Fig. 35.—Villechaise and Jean's operative procedure for syndactyly.

When all four fingers are involved, J. S. Stone has proposed to make a dorsal incision along the full length of the web between the middle and ring fingers with transverse incisions across the ends, thus forming two quadrilateral flaps with pedicles on the little and index fingers. The webs between the index and middle fingers and the ring and little fingers are cut, and the flaps are wrapped around the index and little fingers. A graft is then applied to the remaining denuded surface and, after healing, the middle and ring fingers are separated. In our judgment, this operation is also inferior to free full thickness skin grafting to be described.

As mentioned previously, the foregoing procedures are for use only in the simpler cases or as supplement to a free full thickness skin graft.

If the syndactylism is due to a simple wide web and there is no increasing deformity of the fingers, it is advisable to delay operation to from the fifth to the twelfth year. If there be considerable deformity present, however, or probability that it will increase, earlier operation should be performed even during the first year of life. Here we refer to an increasing distortion of joint development, contraction of the fingers and impairment of growth seen in closely bound fingers, polydactylism, and those patients in whom the syndactylism is associated with aplasia.

Our operative procedures must end in digits that flex freely, have a mobile covering and have no scars that in contracting will cause disability. In exceptional instances this result may be secured by one of the foregoing methods. Usually, however, to insure this result we transplant free full thickness skin grafts.

We regard the following principles to be essential. Careful consideration should be given before operation as to the advisability of any operative procedures. In certain aplasias with loss of tendons and hypoplastic bones, the function may be impaired. In case of doubt, skin grafting should be done rather than depend on inadequate plastic procedures. The operation must end in a commissure covered by skin with no scars across it. There must be no scar line running down one finger across the commissure and up on the other finger, since such scars contract and reestablish the syndactylism and also impair adduction and abduction of the fingers. Therefore, we seek a zigzag long scar line extending into the palm and dorsum of the hand. In incising the web, care should be taken not to injure the digital nerves and blood vessels. Except in the simplest cases, one side of a finger only should be operated on at one sitting since the vitality of a finger may be jeopardized by accidental injury of blood vessels or by the bilateral compression used in case of skin grafts.

When supernumerary digits are present, they should be removed unless their removal will impair the vitality of the finger or end in distortion.

When free full thickness skin grafts are used, the incision should be carried one-half inch down on the palm and to the head of the metacarpal on the dorsum. The edges of the skin of the severed web should be freed from the underlying connective tissue of the adventitious web if it is bound to it. An accurate pattern of the defect is cut from some flexible material such as waxed gauze, crinoline or tin foil. In making this pattern, consideration should be given to the normal outline of the web. It is noted that the web inclines dorso-proximally from the flexor surface of the palm to the knuckle, and an attempt should be made to restore this anatomic conformation (fig. 36).

An artificial perpendicular dorsopalmar web is unsightly, and is avoided by proper preparation of the bed and particularly by the proper outlining and suture of the skin graft. Special care should be taken in outlining the graft not to turn the pattern over, otherwise a negative of the pattern will be secured and the graft will not fit the defect.

The skin chosen for transplant should be thin and hairless. Such skin can generally be secured from the inside of the arm or thigh. In cutting the graft, semicircular tongues should be made on the graft to fit into the incisions prolonged into the palm and on the dorsum. This

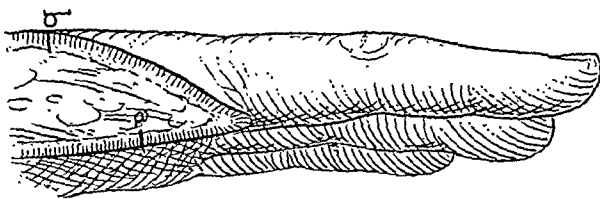


Fig. 36.—Anatomic sketch to show dorsal inclination of the interdigital web and extent of the incision for syndactylism; *a*, palmar; *b*, dorsal.

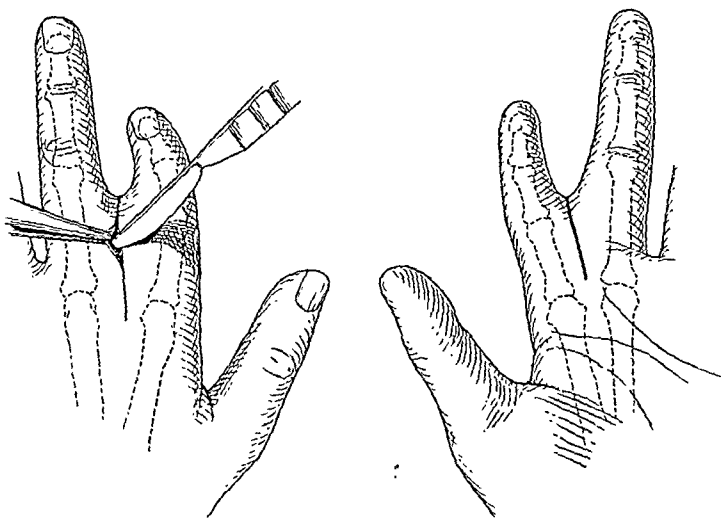


Fig. 37.—Incisions preparatory to free full thickness skin graft.

insures a skin-covered commissure and an irregular elongated scar line, which even though contraction takes place will not end in contraction of the fingers or return of the disabling web. To restore the normal dorso-proximal inclination of the web, the two arms of the graft extending from the new web should be cut in the form of an obtuse angle of about 130 degrees (figs. 37 and 38).

The graft should be trimmed close and applied with pressure sponges and dressings after the careful technic imperative in free full thickness skin grafting, especial care being used to see that adequate separation and pressure are applied at the web to insure free motion at the metacarpophalangeal joint and the dorsal inclination previously mentioned.

When a simple wide web is present, one of the earlier plastic methods may be used if by it one may be sure of a skin-covered commissure and no restriction of motion, although even here the skin graft is often found advisable since after incision the defect is generally greater than had been anticipated. When a skin graft is applied and there is a wide web, one may be able to incise the web anteriorly and posteriorly close to one finger and suture the two flaps about the other with a skin graft applied to the remaining defect on the first finger and over the web.

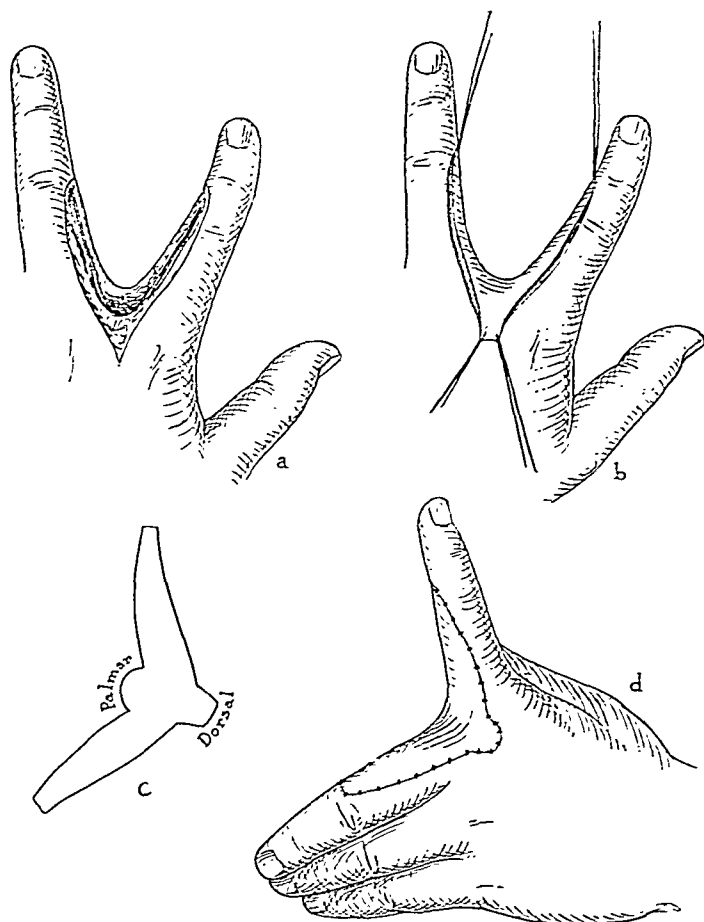


Fig. 38.—Application of free full thickness skin graft. Note the shape of the graft (c).

Here also the incisions should be carried well proximally and tongues of skin should be applied on the palmar and dorsal surfaces as previously suggested. If a graft to the sides of both fingers is anticipated, the web is cut down its middle line. If three fingers are involved, a simple plastic operation may be done between two of them and a skin graft between the other two since it is desirable to avoid a graft on two sides of the same finger, because of fear of impairing the vitality of the finger by pressure on its two sides. If all four fingers are involved, it is better to operate in two stages, treating the web between the index

and middle fingers and the ring and little fingers at the first and that between the middle and ring fingers at a later time. When the syndactylism is between the index finger and the thumb, a wide flap sufficient to permit full extension and abduction of the thumb is imperative. This should be lapped widely on both the dorsal and palmar surface, normal skin being incised if necessary to permit this freedom of motion. In the thumb-index syndactylism particularly the surgeon should not attempt simple plastic procedures unless they will insure perfect mobility.

When terminal bone syndactylism is present, repair by free full thickness skin graft is the ideal procedure (figs. 39 and 40). In these

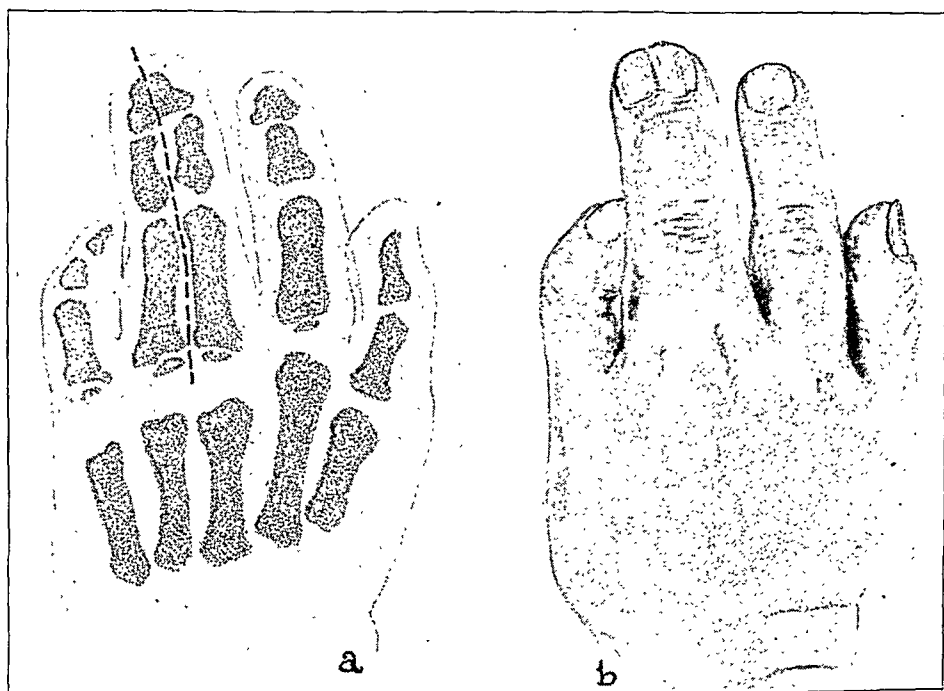


Fig. 39.—Sketch of the hand with complete fusion of the distal phalanges (third and fourth) with fusion of the tendon sheath, but separate tendons, and clinodactylism (fifth) in case 14. The line of separation of fingers is shown in *a*.

cases particular care must be exercised not to injure the blood supply and nerves since they are generally atypical in their division and distribution. Also attention should be given to the tendons and tendon sheaths. If the tendons to the two fingers lie in a common sheath, simple longitudinal through-and-through incision of the common sheath between the two tendon groups is all that is necessary. The two sheaths thus formed cannot be sutured longitudinally, but the applied skin graft will close the sheaths and work satisfactorily. If one or the other of the tendons is incomplete, some judgment is called for in the decision as to which digit the complete tendon should remain attached. In case

the decision lies between the thumb or index finger, naturally the thumb would be chosen and any plastic operation on a tendon, if done, would be applied to the least important digit, here the index finger (case 32). When the nail is fused it may be split longitudinally with the distal phalanx, if the distal interphalangeal joints are separate, and complete function will be restored by bringing the skin graft to the end of the finger. Even in partial fusion of the joint, considerable function may be retained by splitting the joint and phalanx longitudinally. Here, however, the attachment of the tendons must not be overlooked. When marginal aplasia is associated with extensive syndactylism, it is surpris-

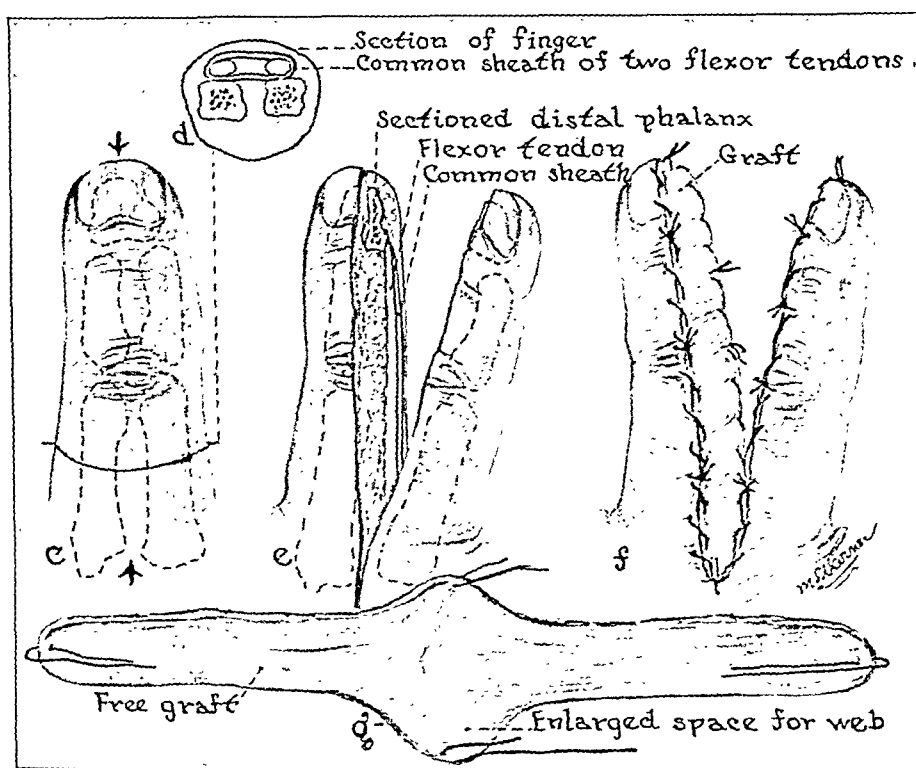


Fig. 40.—Sketch of operative procedure in case 14. (See fig. 30.) Note the common sheath for the two tendons in *d*.

ing how much function can be secured by skin grafting in stages, particularly in the fingers (fig. 41). There is generally some tendon attachment, and when the aplasia is of the distal phalanges alone considerable mobility of the individual fingers can be secured; when the aplasia involves the middle phalanx, but little flexion of the fingers can be expected since there is commonly intra-articular or periarticular disorientation leading to permanent disability. The fingers can be made more slightly, however, and the function can be increased somewhat. When the aplasia is on the radial side with involvement of the thumb, there is not infrequently disorientation of the intrinsic muscles of the



thenar group with permanent impairment of function. Here especial care should be given to securing stability of the thumb and function of the flexor longus and brevis pollicis. This comes under consideration particularly in connection with extensive central aplasia (lobster-claw hand) where there may be serious disorientation of the structures of the thumb. Here, if there is good function in the index finger-thumb syndactylized group with great disorientation, separation of the two should be decided on only after serious consideration. In several central aplasias with lateral syndactylism we have, however, been able to secure considerable cosmetic and functional improvement by skin grafts between the thumb and index finger and the ring and little finger with a central suture bringing the separated index and ring fingers together (see case 30, fig. 17).



Fig. 41.—Complete distal aplasia and syndactylism of all digits in case 23. The roentgenograms were made before and after operation and the photograph after free full thickness skin grafting between aplastic digits.

In the complicated cases with disorientation of joints and the surrounding tissue, splinting and physical therapy may be necessary to secure the best results.

### POLYDACTYLISM

It is in polydactylism particularly that proponents of the theory that congenital malformations arise as a reversion to type think they find support, but attention has already been drawn to the fact that Prentiss and others have found in embryology, paleontology, comparative anatomy or the phylogenetic history no basis for this assumption. The presence of polydactylism in Lineback's 22 mm. embryo and Schoo's 9 cm. embryo should disprove the possible etiology from amniotic bands. It is, therefore, reiterated that the only reasonable assumption is that it arises as a disorientation of embryonal tissue originally activated from

the germinal cells. This disorientation is of a slightly greater degree than that giving origin to simple syndactylism and one that involves the bone anlage in addition to the superficial structures. It is a not uncommon accompaniment of syndactylism and may be associated with aplasia of part of the hand although this is less common. As we would expect, the disorientation of bone anlagen that produces polydactylism not uncommonly ends in hyperphalangism, both latent and manifest, symphalangism and clinodactylism. Polydactylism is very frequently symmetrically bilateral, has a history of it or allied lesions running through several generations and often is associated with somewhat similar lesions affecting the feet, especially the radial side. It is not infrequently associated with other congenital malformations such as acrocephalia, scaphocephalia, harelip and various other lesions.

Polydactylism is seen in two general types, the first represented by the dichotomy, partial or complete, of the individual digits, the second by the so-called mirror hand. The first is the common type. In this any or all the fingers may be involved. Generally, however, the involvement is more simple, and most often it is seen in one of four groups: involvement of the little finger alone, of the middle and ring fingers, of the index finger or of the thumb. The first, third and fourth groups are the most common.

The little finger presents the simplest type. There may be a complete separation into two digits, with or without syndactylism and at times with a fully developed extra metacarpal. Generally, however, the added finger is aplastic with no tendon supplying it and having only atypical rudiments of bone. Not infrequently simply tags of skin and subcutaneous tissue attached to the base of the finger or the ulnar side of the hand (case 48) are seen. The metacarpal may show beginning distal dichotomy, and the ulnar carpal bones may be atypical.

A more complicated type is that seen when the middle and ring fingers are involved. While complete separation may occur, syndactylism between the partially or completely formed extra digit and the other digits is generally present. The extra digit is generally very atypical as to form, development of nerve and blood vessel supply and tendon attachment. The joints are often atypical. The parent digit, while often complete, not infrequently presents joint distortion, latent and at times manifest hyperphalangism. Partial polydactylism as represented by division of the distal phalanx alone is not so common as in the thumb. There may be reduplication of the metacarpals, but, if involved, one more often sees distortion of the epiphysis or distal bifurcation (figs. 42 and 43). The syndactylism so obscures the lesion that the incipient cases of polydactylism may be overlooked unless x-ray pictures are taken. As would be expected from the common embryologic origin of the little, ring and middle fingers, these three may be associated in disorientation.

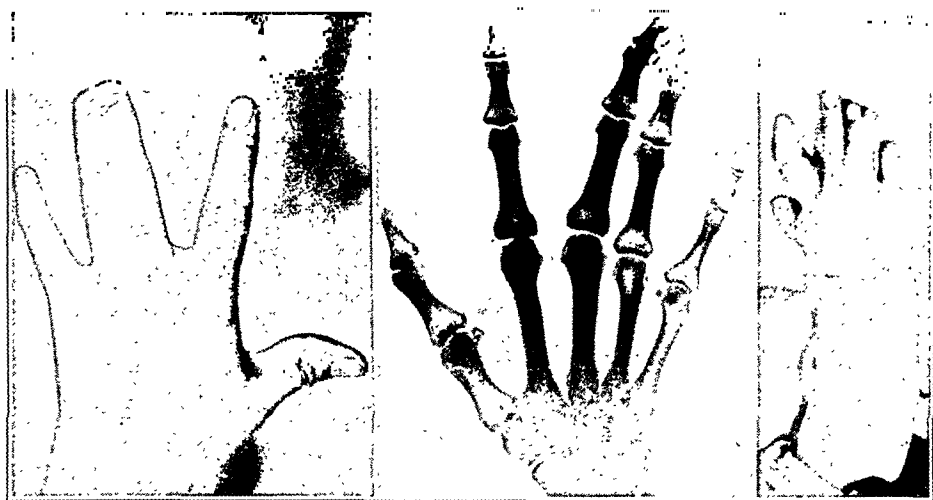


Fig. 42.—Polydactyly in father and son (cases 15 and 16).

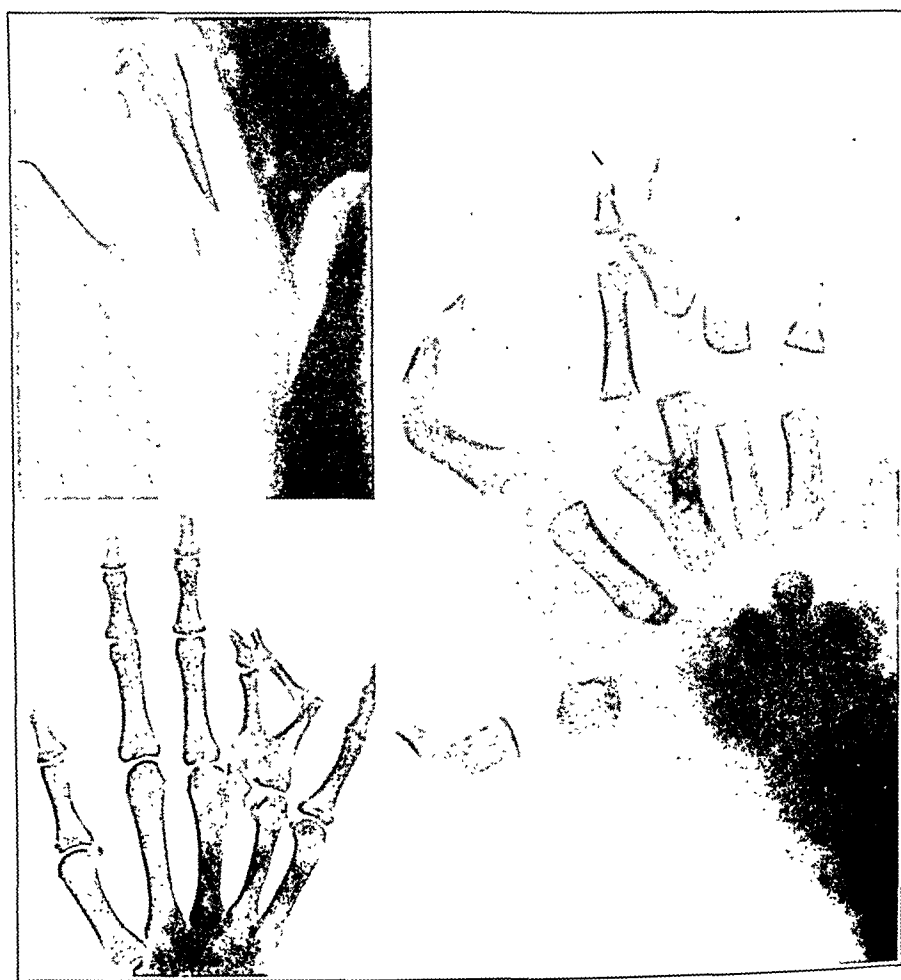


Fig. 43.—Polydactyly in mother and daughter (cases 18 and 19).

When one considers polydactylism of the medial element or index finger, there is considerable confusion, and often one hesitates to say without dissection which would reveal muscle attachments whether an extra digit lying to the radial side has its origin from the index finger or the thumb. This confusion arises from the fact that hyperphalangism of the thumb is not uncommon, and a careful survey of the cases reported convinces one that in some instances triphalangeal thumbs have been called extra index fingers, and that the converse is also true. It is our belief that polydactylism in the index finger is less common than in the other digits. Surely not a great number of atypical rudimentary forms are found.

Polydactylism of the thumb is an especially interesting study. Attention has already been drawn to the frequency of hyperphalangism of the thumb and the interesting questions as to whether the metacarpal is a real metacarpal or a proximal phalanx. Owing probably to the fact that the thumb is the only digit having origin in the radial element, it presents polydactylous forms peculiar to itself, as, for instance, the frequency of dichotomy of the distal phalanx, hyperphalangism, its not infrequent division into three partial or complete digits and the substitution for it of a mirror hand in cases presenting this malformation. The disentangling of these complex pictures often presents difficulties.

Partial or complete bifurcation of the distal phalanx is fairly common (fig. 44). The extra phalanx and normal phalanx may be of equal or unequal sizes. The atypical phalanx may be on either side, but is generally on the radial side. If there is a greater separation of elements, generally one or all are atypical. If two, the more atypical generally lies to the radial side; if three, it is not uncommon to see the best developed digit triphalangeal and lying between two markedly atypical rudiments. However, almost every degree of development of the two or three digits may be seen. Extra metacarpals may be present or the one may be bifurcated. Syndactylism between the distorted digits is often seen.

As examples of these forms the following may be mentioned:

SPRONCK.—Two metacarpals present, with a two phalangeal digit attached to the outer one and a three phalangeal digit to the inner one, the two being bound together in syndactylism.

WINDLE.—Right hand, triphalangeal thumb in syndactylism with index finger; left hand, the same condition with two rudimentary phalanges attached on the outer side to the normal metacarpal.

CARRÉ.—Double radius probably and probably three fairly normal thumbs.

BATESON.—Triphalangeal thumbs, bilateral, with two rudimentary phalanges on the inner side attached to a normal metacarpal.

RUDINGER.—Bilateral, double triphalangeal thumbs.

GRUBER.—Extra triphalangeal digit close to the index finger; triphalangeal digit external to this, surely a thumb, having on its outer side a rudimentary two phalangeal digit attached to the thumb metacarpal. It is really impossible here to be certain whether the first named extra digit is a thumb or a reduplication of the index finger.

HARKER.—Right hand, triplicate thumbs each with three phalanges and three nails bound in syndactylism; left hand, double thumb with two sets of phalanges and two nails bound in syndactylism.



Fig. 44.—Polydactylism of the first and fifth digits with a schematic drawing illustrating origin from embryonal disorientation (cases 49, 50 and 51).

DESMOYERS AND ILL.—Right hand, triple thumb; left hand, double thumb. The triple thumb has one metacarpal and from it extends an outer atypical biphalangeal digit, a middle triphalangeal digit and an inner triphalangeal digit.

These examples illustrate some of the many forms seen. The variability of muscle growth and attachment is shown by Gruber's anatomic study of seven cases with double thumbs. In these the muscular attachments were as follows: The flexor longus pollicis was attached to both thumbs in all cases, but was not always equally developed; the flexor longus pollicis was commonly attached to the median, and in only two cases to both elements; the flexor pollicis brevis as a rule was attached to

the lateral, but in one case to median only, and in another to both; the adductor brevis pollicis was constantly attached to the lateral, but in two to the median also; as to the adductor pollicis longus, in three cases it was attached to the lateral; the opponens pollicis was attached in two cases to the lateral and in one to the median. It is, therefore, evident that in cases with two or three fairly well developed radial digits, operative procedures should not be entered on without due consideration.

The radial metacarpal and carpal bones may partake in the reduplication.

When the etiology and pathology of double major buds, the arm, forearm or hand (fig. 45), are considered, a strange phenomenon is encountered. Instead of the simple reduplication or formation in suc-



Fig. 45.—Mirror hand and forearm, with a schematic drawing illustrating the manner of origin in case 52.

cession as seen in the digits, there is a strong tendency to asymmetrical development, the so-called mirror arm or hand. Bateson<sup>11</sup> made the first comprehensive analysis of these cases. From his studies he established the law that two adjacent members form in structure and position the image of each other as reflected from a plane mirror bisecting the angle between the respective axes and perpendicular to the common plane of the two axes. Almost without exception the double limbs in man have been found to follow this rule; various numbers of digits are found, more commonly six, seven or eight, the radial parts of the forearm being lost and the two ulnar parts being joined in the same plane or at an angle. The fact that the ulnar parts may join at an angle has often led the observers to state that the extra fingers in the radial arm

11. Bateson, William: Materials for the Study of Variation. New York: Macmillan Company, 1894.

function as a thumb. It is clear, however, that these extra fingers are in no sense related to the thumb, but their assumption of thumb function is simply an accident of incomplete rotation.

This phenomenon of the inherent tendency of buds to rotation has excited the attention of many biologists, and from experiments by Harrison, Swett, Detweiler, and others on *Amblystoma*, *Triton constatus*, *Diemyctylus viridescens* and other lower forms of life, many interesting facts have been deduced.

In these experiments the limb bud or parts of it have been excised, transplanted to the same side, or the opposite side, rotated in its original location, split in situ in various planes, and yet the bud is found to contain this inherent tendency to rotation.

Harrison<sup>12</sup> showed that even a few cells of the embryonic rudiment have the power to produce a complete appendage if grafted on a favorable location, thus showing that the forces that determine polarization of the anteroposterior axis reside within the limb mesoderm itself. Morgan takes the view that the molecular constitution of the egg contains the potential factors of symmetry. Conklin and Lille showed that polarity resides in the ground substance of the cells.

Harrison's rules for transplantation are stated as follows:

1. A bud that is not inverted (dorso-dorsal) gives rise to a limb of the side of origin of the bud whether implanted on the same or the opposite side of the body.
2. An inverted bud (dorso-ventral) gives rise to a limb of reversed asymmetry whether implanted on the same side or the opposite side of the body.
3. When double limbs arise the original one (the one to first begin its development) has its asymmetry fixed in accordance with rules 1 and 2, while the other is the mirror image of the first.

It is interesting to note that in case the second bud itself is doubled, then this third bud is a mirror of the second. But now comes Swett<sup>13</sup> with experiments to prove that he can produce 100 per cent of exceptions to Bateson's law that two adjacent members form images of each other. This occurs in those instances in which the graft comes off from the primary bud and is well separated from the primary cells of the arm bud. In other words, we must conclude that "two limbs of the same asymmetry may stand in series (not mirrored) either as a result of independent origin and development from isolated fragments of the same or different harmonic limb rudiments or in case one or more arises from a disharmonic rudiment in consequence of successive rotation and reduplication phenomena." The property of rotation seems to be in some way lost when the reduplicated bud is disassociated from the primary cells of the rudiment bud.

12. Harrison, R. G.: Experiments upon the Development of the Forelimb of *Amblystoma*: A Self Differentiating Equipotential System, *J. Exper. Zool.* **25**:413, 1918; On Relations of Symmetry in Transplanted Limbs, *ibid.* **32**:1, 1921.

13. Swett, F. H.: Experiments in Splitting the Regenerating Limb Bud, *Anat. Rec.* **40**:297, 1928; reference given here to his other contributions.

The last word in this complex problem of rotation has not been said, but that major limb buds tend to rotate while buds from subordinate division do not have such tendency, has abundant clinical support.

Our own case is one with eight fingers, the radial four being mirrors of the ulnar four, the series running as follows: fifth, fourth, third and second and second, third, fourth and fifth. There is also an absence of the radius and a reduplication of the ulna, with some disorientation of the elbow joint and a partial distal reduplication of the humerus with some disorientation of its distal end (see fig. 45, case 52). A reduplication of metacarpals and carpals occurs in the same mirror form. A summary of some of the various types recorded in the literature illustrate the general picture:

MURRAY.—Right, normal; left, eight fingers, mirror hand, with wide space between the groups; some syndactylism between fingers.

FUMAGALLI, GIRALDES.—Left, normal; right, same as Murray's case except no syndactylism.

DWIGHT.—Right, normal; left, double ulna; unciform, os magnum, cuneiform, double; semilunars fused; seven metacarpals and seven fingers, fifth, fourth, third, second—third, fourth, fifth.

BALLENTINE.—Same as Dwight's case except left normal and right involved with some syndactylism.

JOLLY.—Right, normal; left, six fingers, fifth, fourth, third—third, fourth, fifth, but the third of the added hand appeared to be a double finger in fusion.

KUHNT and EKSTEIN.—Cases with five fingers, but bilateral in each instance, fifth, fourth, third—fourth, fifth. In Kuhnt's case the feet were similarly affected.

GHERINI.—Bilateral six fingers, fifth, fourth, third—third, fourth, fifth; each foot with nine metatarsals and nine digits in mirror form.

Various other combinations are reported. Syndactylism is not uncommon. Some aplasia may be seen and, if present as a biphalangal digit in the adventitious index finger, has given rise to the erroneous assumption that the aplastic finger is a thumb. The position of the rotated hand may vary, but not uncommonly there is sufficient flexor angulation to permit a portion of the hand to function in apposition to the primary hand in the manner of a thumb.

#### TREATMENT

Before decision is made as to advisability of operation, careful consideration should be given as to function that will be retained or secured. Attention has already been drawn to the atypical position of nerves, blood vessels and tendon attachments. The tendons may or may not reach the terminal phalanx of the digit that is preserved. Especial care should be exercised in the thumb since here the atypical form and attachment of the intrinsic muscles of the thenar area are conspicuous (*Gruber, vide supra*) and a flail digit is worse than useless.



This is particularly emphasized since thumb apposition is most important. It may be found advisable to preserve a syndactylized extra digit to maintain function. When aplastic extra digits are present simple amputation is generally advisable, and the same is true of unsightly extra digits, the presence of which adds nothing to the function. When syndactylized extra digits are present they should also be removed for cosmetic reasons if their removal will not damage the action of the hand. At times, especially in the thumb, it may be necessary to transfer a tendon or muscle attachment from an atypical extra digit to the remaining digit. This necessity is met with in both the fingers and the thumb. In exceptional instances in case of the thumb it may be necessary to transfer a tendon from another part of the hand. When an extra digit with a bifurcation of the metacarpal or a large metacarpal is present, it may be advisable to remove the extra metacarpal growth.

In case of bifurcation of the distal phalanx particularly, impaired function may result if one of the parts is removed *in toto*, due to loss of tendon and joint function. This is particularly true in the case of

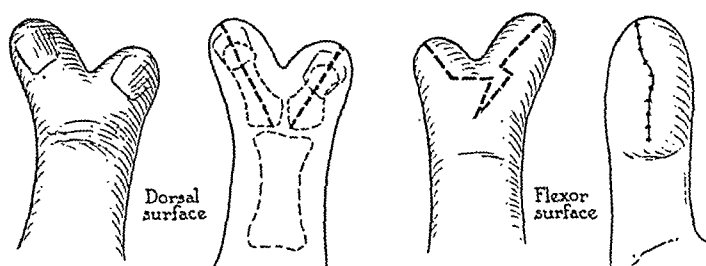


Fig. 46.—The Bilhaut-Cloquet operation for bifid thumb.

the thumb. When one part is very rudimentary its removal may be indicated; if, however, after examination it is found that joint or tendon function will be impaired a plastic procedure (Bilhaut, Cloquet) is indicated. This consists of removing a V-shaped medial section from the two parts. The incision extends from the middle of the distal part of one rudiment down to below the bifurcation and back distal to the middle of the other rudiment; the intervening bone, skin and connective tissue is removed and the remaining parts are sutured together in the midline, thus restoring a normal distal phalanx. If one is somewhat shorter than the other, a zigzag incision is made on the flexor surface, the long arm being on the short rudiment. Figure 46 illustrates the procedure.

#### HYPERTROPHY (MEGALODACTYLISM, MACRODACTYLISM) ARACHNODACTYLISM, MULTIPLE CARTILAGINOUS EXOSTOSES AND OTHER OVERGROWTHS

The orientation of hypertrophy of the fingers with other congenital malformations of the hand presents considerable difficulty. One cannot be certain whether he is dealing with a process peculiar to the hands or one correlated with other forms of hypertrophic growth about the body.

Against the assumption that it is related to the other malformations peculiar to the hand is that it is practically never hereditary, one case only being reported; that it is seldom associated with other congenital lesions, a very few cases only of syndactylized fingers are found, and that it is seldom bilateral. Also, one remembers that hypertrophy of individual bones in other parts of the body is often reported, such as the clavicle, hyoid, superior and inferior maxillae, zygoma, tibia, various cranial bones, etc. Thus its relation to a common genesis with fibromatosis, leontiasis ossea, angiomas, arachnodactylism and multiple cartilaginous exostoses cannot be lightly cast aside.

On the other hand, Wieland found in an hypertrophy an abnormal early appearance at ten months of a bony center of growth in a very large epiphysis, and an examination of the cases presenting latent and manifest hyperphalangism would lend support to the assumption that hypertrophy has a distinct relation to disorientation of bone anlagen possibly activated by disturbance of the germ plasm. Ductless gland perversion or disturbances of the central nervous system seem too general for an isolated lesion. We have placed it among the cases of mild disorientation, but wish here to record our uncertainty as to its exact origin and relation to the other deformities. The same should be said regarding lymphangioma, blood vessel angioma, neurofibroma, arachnodactylism, multiple cartilaginous exostosis and other types of overgrowth.

#### HYPERTROPHY

Hypertrophy of the digits is not commonly seen, less than 75 cases being reported. It involves especially the thumb, index and middle fingers. These may be involved individually or together. Our own case, seen through the courtesy of Dr. Kellogg Speed, showed involvement of the thumb and index finger of the right hand (fig. 47). Kilinger's bilateral case involved the first, second and third digits of the right hand and the first and second digits of the left hand, while Mouriquand and Buche's case involved the first, second and third digits of the right hand and the fourth and fifth digits of the left hand.

Megalodactylism appears in two types: that due to bone growth alone, illustrated in figure 47, and that due to neurofibromatous and lymphatic overgrowth, especially the former, illustrated by our second case (fig. 48). There is very little overlapping in these forms. Those due to bone overgrowth seldom show any peculiar change in the soft tissues. The three phalanges are commonly involved to the exclusion of the metacarpals; some disorientation of the epiphyses is commonly present, distorting the contour of the joints and ending not infrequently in lateral curvature of the digit. The x-ray picture of the bone is fairly normal in most cases with an added area of density of the cortex and some broadening of the cartilage and changes in the epiphysis. There is often an increase of subcutaneous fat.

When megalodactylism is due to neurofibromatosis, the appearance is so similar to that produced by bone overgrowth that often a roentgen examination is necessary to differentiate them. Few changes in the bones are seen.

*Treatment.*—Where there is bone overgrowth no treatment is indicated, except for the unsightliness or because of impaired function of the hand. Here partial or complete amputation is indicated. If the overgrowth is due to neurofibromatous tissue, function and cosmetic improvement can be secured by a removal of the excessive tissue, as was done in our own case.



Fig. 47.—Hypertrophy of the index and middle fingers. (Courtesy of Dr. Kellogg Speed.)

#### ARACHNODACTYLISM

Arachnodactylism is characterized by a striking increase in length of the bones of the hand without growth in breadth. It seems more certainly to be associated with some general disorientation of tissue probably having its origin in the germinal center. Some think it is a disorientation of the mesoblastic tissue generally. While the appearance of the long slender hands—often with flexed fingers due probably to growth of the bones in excess of that of the tendons—is characteristic, there are in addition an elongation of other bones, an undeveloped musculature of the entire body, congenital heart disease, infantilism, congenital dislocation of the lens and other ocular impairment. One must, therefore, search for the etiology along with that for the group of lesions such as achondroplasia, mongolism and perversions due to disturbance of the endocrine system.

## MULTIPLE CARTILAGINOUS EXOSTOSES

In multiple cartilaginous exostoses more or less symmetrical benign cartilaginous growths are found in the hands and other parts of the skeletal system. Runecke, in 1890, collected references to 36 families in which 172 cases occurred. In one instance the disease was shown in

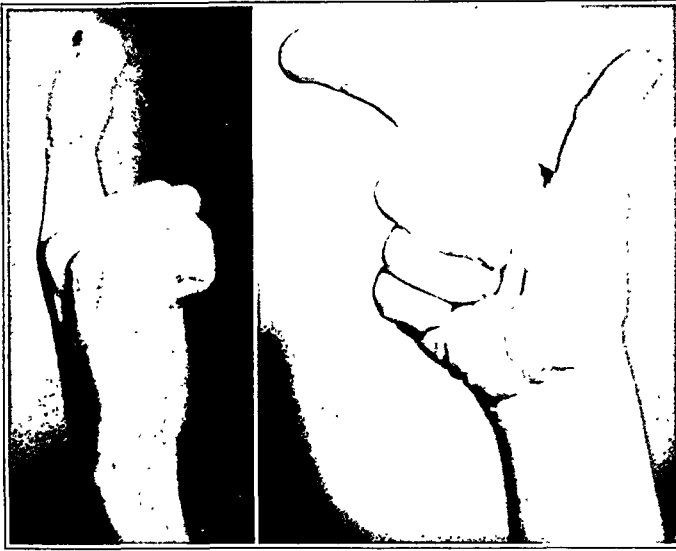


Fig. 48.—Spurious hypertrophy in case 59. There is no change in the bone. The enlargement is due to neurofibromatous tissue.



A A B  
Fig. 49.—Disorientation of soft tissue. *A*, case 55 and *B*, case 56.

five generations. Ehrenfried collected 236 cases reported since 1890, in which heredity was noted in 176 cases. Shortness of stature is generally present and is due usually to lack of growth of the legs. There is often a relative shortening of the ulna producing a dislocation of the radius

at the upper end, often miscalled congenital dislocation of the ulna. Changes in other bones are noted.

It would carry us too far afield to do more than mention the great number of anatomic variations in the origin and insertion of muscles, presence of atypical muscles, atypical nerves and blood vessels. In general, they must be ascribed to tissue disorientation originating in the germinal cells.

Congenital club fingers have been reported in several instances, as a family trait. Siemens studied a family in which the lesion ran through five generations. The enlargement is generally due to overgrowth of the soft tissue, often a neurofibromatosis.

Scleroderma, loss of nails and other cutaneous lesions have also been noted as congenital lesions.

#### CONTRACTURES OF HAND AND FINGERS

Congenital contractures of the fingers or hand are not uncommon and are generally due to disorientation of various structures in the hand. Figure 49 illustrates two of the many types seen. Deviation of the fingers to the ulnar side and in flexion is most common. Some cases reported have been due to nerve injury at birth, but many are definitely associated with changes of undoubted germinal origin. Manson's patient with bilateral deviation of the fingers to the ulnar side had also bilateral brachydactylism of the thumbs. Our own cases also had associated changes (fig. 49).

#### SUMMARY

A critical analysis of cases with congenital malformations of the hands leads us to eliminate amniotic bands, reversion to type and all other suggested etiologic factors except impairment of the germinal cells as the activating source of these malformations. A study of the embryology and its correlation with clinical cases leads us to classify the lesions in simple anatomic groups and to eliminate the classifications based on individual clinical cases. This simple classification is shown to comprise all cases and make their origin, nature and relationship understandable. Briefly, we may say:

Congenital malformations of the hand are due to varying degrees of growth impairment having origin in the germ plasm.

Moderate growth impairment ends in tissue disorientation.

Severe growth impairment ends in aplasia and hypoplasia.

Either type may involve the whole extremity or any embryologic subdivision.

Anatomically, these types may involve: (a) the upper part of the arm or whole arm, (b) the radial bud and its radicle in whole or part and (c) the ulnar bud and its radicles in whole or part.

Technical procedures that have been found advantageous in the treatment for aplasias, syndactylism and other malformations have been presented with illustrative cases.

# TUMORS OF THE SMALL INTESTINE

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*(Concluded from page 177)*

## RARE TUMORS

### ENTEROCYSTS

Cysts of the intestine are exceedingly rare, and few cases have been reported in the literature. One case only was found in this clinic, occurring in the duodenum of a 3 day old child. The age of incidence has little bearing on the condition. If one accepts the congenital theory of origin, cysts undoubtedly exist from birth. Therefore in cases in which they are symptomatic, clinical recognition occurs early. Asymptomatic cysts, on the contrary, are not recognized until after death. Cysts occasionally are found in the duodenum. Such were the foregoing case and that of Vogt. The site of election, however, is the ileum near Meckel's diverticulum.

The gross pathologic process is variable. The cysts may be multiple or they may occur singly. They rarely are larger than a walnut, although cysts as large as a man's head have been reported. The tendency is toward the external type in the ileum, although internal cysts are not unknown. They are often confused clinically with ovarian cysts. Elsewhere in the intestine, the internal form is most commonly found. The cyst is fluctuant to touch and is surrounded by a glistening bluish membrane. The contents may be mucilaginous, gelatinous or fluid in consistency, and colorless, yellow or brown. The cyst wall is reduced to a collapsed sac when the contents are expressed.

The microscopic section of the cyst wall shows it to be composed in some instances of all the layers of the intestinal walls. It is lined by a single layer of epithelium, which may be columnar, cuboidal or stratified. Many variations of this picture may be seen. Any of the layers may be absent, or the wall may be composed of a single layer of epithelium alone, supported by thin strands of connective tissue or muscle fibers.

The origin and histogenesis of intestinal cysts have been subject to much discussion. Vogt believed his case to have arisen from a remnant of the wolffian body, and, so far as is known, it is the only one of its kind. He ascribed its development to a cellular hyperplasia coincident with the regressive changes of the wolffian body, and compared its pathogenesis to that of teratomas. The most popular theory of

origin is that of incomplete closure of the omphalomesenteric duct in the embryo. Hamilton, naming the anomalies of closure that may occur, stated that closure at both ends with patency between may later result in a cystlike dilatation. If this dilatation is at the junction of the duct with the intestine, it is termed an enterocyst. Slesinger suggested the possible origin from a distended mucous gland, but there is insufficient evidence to support his theory. Other writers believe that the cyst is primary in the mesentery and secondary in the intestine. Keibel and Mall described a vacuolation of the intestinal epithelium opposite the mesenteric attachment in the region of Meckel's diverticulum, which Theis regarded as the anlage of enterocysts. One can only deduct at best that evidence points toward an anomaly of embryonic development as the most logical explanation.

#### CYSTIC PNEUMATOSIS

The unusual condition of cystic pneumatosis is not an infrequent occurrence, but is of interest primarily from the pathologic aspect, since it is almost solely confined to oriental countries. It was first described by Colquet and Dulaney in 1825. Weil was later able to collect seventy cases from the literature. Briefly, cystic pneumatosis consists of the appearance of multiple gas-filled cysts on the serous surface of the intestines. Appendicitis, peritonitis or obstruction with distention and tympanites may be simulated clinically.

The disease is most prevalent among middle-aged men inhabiting Asiatic countries. It is not restricted to any part of the bowel, the whole intestinal tract being affected.

The most interesting clinical feature is the manner of onset and the course. The condition appears and subsides spontaneously, lasting from a few days to a week. During the height of the symptoms, operation is usually performed for obstruction.

When the abdomen is opened, all of the intestines are seen to be covered by grayish-white, transparent cysts filled with gas. They vary in size from that of a pinhead to that of an orange. They may be discrete or confluent, and sometimes resemble a cluster of grapes. The intestinal wall is thickened, boggy and crepitant to touch. If it is pricked, the cyst collapses, leaving a thin sac. A small amount of purplish fluid has been found in some of the cysts in addition to the gas.

Microscopic examination of the cyst wall may show the presence of the outer layers of the intestine. More commonly the gas originating in the submucosa works its way through to the subserosa and then balloons the serosa outward alone. It is hypertrophied and lined by a single layer of epithelium. There are marked edema, a slight excess of fibrous tissue and many giant cells. Malignant degeneration has never been noted.

Although the cystic formation has been thoroughly studied, no satisfactory conclusions have been reached in regard to its etiology. No communicating orifice has been demonstrated between the lumen of the intestine and the cysts, in spite of the fact that the gas appears and disappears without reason. Leffer and Tull analyzed the gas and found it to consist largely of hydrogen and carbon dioxide. The gas is not toxic and does not produce peritonitis. Bubis and Swanbeck suggested among other theories of origin that of a mechanical permeation as the most plausible. They expressed the belief that it is brought about by increased pressure within the bowel, forcing gas through the most vulnerable points of the inner layers of the wall. This view, in consideration of the characteristics of the gas and its formation, is most commonly accepted.

#### NEUROBLASTOMAS

In 1925, Ritter described two cases of a tumor that he termed neuroblastoma. His are the only cases reported in the literature, although it is his opinion that others have passed as a type of sarcoma since the resemblance is striking. The origin is thought to be from the chromaffin cells of the autonomic nervous system, but the etiology and development are obscure. Both cases occurred in young people, and he regarded them as rare in adults.

The tumor is definitely invasive in type. It grows through all coats of the intestine, presenting on both mucosal and serous surfaces. The shape is irregular and may resemble carcinoma in gross section. The consistency is firm, or, if necrosis has begun, the tumor may be friable. One of the cases had undergone necrosis with cavitation. The color is usually white with a pinkish tint.

The tumor, as described by Ritter, is composed of numerous small round cells resembling those of the lymphoid series. They contain very little cytoplasm, and the nuclei are small, dark and rich in chromatin. The cells occasionally show an acinar arrangement, being polarized about a central mass of finely granular material. Larger cells are sometimes seen that show mitotic figures. Giant cells are not rare. Pyriform cells may be found with a delicate stellate cytoplasm. The picture bears a striking resemblance to that of spongioblastoma.

No cases have been observed in this clinic, and it has been impossible to study them. From the description just given, however, it seems possible that these tumors resemble and may have passed as members of the lymphoblastoma group.

The prognosis of benign tumors as a whole is good. The percentage of mortality of the symptomatic tumors in this group was found to be 25 per cent. This figure included all deaths due to postoperative complications or other intervening causes. Secondary complications, such as



acute obstruction and peritonitis from gangrene and perforation, were undoubtedly responsible for a large number of the deaths. In the absence of such complications, excision of the tumor or resection of a piece of bowel with good surgical technic should insure complete and permanent recovery.

### SECONDARY TUMORS

The small intestine is not an uncommon site for metastases from primary malignant growths located elsewhere in the body. Secondary growths are given consideration in this paper because of the interest they arouse by simulating primary growths. For this reason it is important to be familiar with the parts of the body from which tumors are most likely to metastasize and the regions of the intestine that are most frequently the seats of these secondary growths. It is also of interest to know the types of neoplasms forming the secondary tumor

TABLE 5.—*Locations of Primary Growths*

Stomach.....	10
Pancreas.....	8
Uterus.....	6
Mesenteric glands.....	4
Colon.....	3
Skin.....	3
Liver.....	3
Gallbladder.....	3
Breast.....	2
Testicle.....	2
Peritoneum.....	1
Orbit.....	1
Bladder.....	1
Cervical glands.....	1
Pleura.....	1
Suprarenal gland.....	1
Total.....	50

and by what means the tumor has been transported. Fifty secondary tumors of the small intestine were studied, and while this by no means comprises the entire list, it is taken as a basis for comparison. The aforementioned statistics are represented in tables 5, 6, 7 and 8.

The stomach is the most common site for the primary growth, a fact that is probably accounted for by the prevalence of cancer in that organ. The pancreas and uterus follow closely in frequency, since they, too, are common locations for abdominal tumors. It is to be noted that in only five cases was the primary tumor located above the diaphragm. This indicates that the metastasizing cells are carried largely by the lymphatics.

Table 6 is self-explanatory. It is peculiar that only one metastasis took place to the jejunum, while the duodenum and ileum were so frequently invaded. The secondary tumors were multiple, as is to be expected in a large percentage of the cases.

The prevalence of carcinomas among all malignant tumors is clearly shown in table 7. Sarcoma is fairly common. The single instance of

teratoma was unusual in that the primary growth was in the testicle and had undergone malignant degeneration.

Secondary invasion is approximately equally divided between extension and metastases. The former, as may be supposed, however, occurred only from primary tumors in other abdominal organs.

One should always bear in mind the possibility of a primary focus elsewhere when the symptoms and signs point to a neoplasm in the small bowel. Careful examination, considering the frequency and figures just quoted, will undoubtedly prevent embarrassing oversights in certain instances.

TABLE 6.—*Locations of Secondary Growths*

Duodenum.....	16
Jejunum.....	1
Ileum.....	15
Multiple.....	16
Undetermined.....	2
Total.....	50

TABLE 7.—*Types of Secondary Tumors*

Carcinoma.....	39
Sarcoma.....	10
Teratoma.....	1
Total.....	50

TABLE 8.—*Method of Transportation*

Metastases.....	26
Extension.....	24
Total.....	50

### CLINICAL ASPECTS

The clinical recognition of tumors of the small intestine is at best a difficult undertaking. Although definite symptoms are produced, they simulate so closely other intra-abdominal lesions that a correct pre-operative diagnosis is seldom made on the basis of symptoms and physical signs alone. Even in instances in which the clinical picture is relatively clear, the infrequency of the condition alone has no doubt often discouraged the correct diagnosis. Roentgenograms offer the best positive means of recognition, but they are not infallible. Positive findings are of great value, but negative results do not necessarily rule out a tumor. Nevertheless, the importance of a careful roentgenologic examination cannot be overemphasized.

Symptoms and signs are brought about largely by the mechanical condition produced by the tumor, and to a lesser degree by the constitu-

tional effects of the tumor on the patient. On the basis of location, the small intestine is divided into two parts for clinical consideration, the duodenum and the jejuno-ileum. Benign and malignant tumors give rise to somewhat similar symptoms, except in instances in which the latter are sufficiently invasive to cause constitutional manifestations. They are, therefore, discussed under separate headings.

#### DUODENUM

1. *Benign Tumors*.—The picture is practically always that of an obstruction. It is a slowly developing condition caused by gradual and progressive encroachment of the tumor on the lumen.

Symptoms: Pain in the epigastrium is the most constant symptom. It may be cramplike or burning. In the latter, the picture may resemble that of an ulcer, especially if the mucous membrane is eroded over the tumor. The pain may or may not be localized. When limited to the upper right quadrant of the abdomen, it may be confused with an acute attack of gallbladder disease.

Nausea and vomiting are frequent symptoms and usually precede the onset of pain for from two to five weeks. Vomiting is more pronounced as the obstruction increases, and when complete is copious and watery. It may be bile-stained if the obstruction is below the ampulla. Hematemesis is sometimes seen when the tumor is eroded. Dehydration, toxemia, alkalosis and intense prostration are symptoms secondary to the vomiting, and may be marked.

Distention is one of the frequent and distressing manifestations of duodenal obstruction. In the early stages, it may be a mere sensation of fulness in the epigastrium, but later it may reach such a degree as to become oppressive and interfere with respiration.

Diarrhea is often present, but may alternate with constipation. Melena is not unusual and constitutes an important feature of the history.

Malaise and loss of weight are secondary and most marked when the vomiting is severe. Secondary anemia is present in cases of prolonged bleeding, contributing to the condition.

Physical Signs: Tenderness in varying degrees is the most constant physical sign of a tumor of the duodenum. It may be exquisite in some cases or slight in others, being elicited only on deep palpation. It may be limited to the upper right quadrant or diffuse. Rigidity is seldom present unless perforation has occurred. The tumor may be palpated through the abdominal wall, if it is of sufficient size, and when benign is loosely attached and freely movable.

Distention is a marked feature when the obstruction is complete. It is due primarily to dilatation of the stomach rather than of the duodenum. A succussion splash is a valuable diagnostic sign when

present. It consists of a splashing sound elicited by shaking the body sharply from side to side. It occurs when gas and fluid are present together and is one of the most constant signs of gastroduodenal dilatation. Peristaltic waves are occasionally seen or palpated when the stomach is grossly dilated.

The vomitus is thin, watery and of low specific gravity. It contains particles of undigested food, in fact, the food materials from several previous meals, if the obstruction is complete. The acid content may be high and the fluid is bile-stained if the obstruction is below the ampulla. Gross hemorrhage may appear in the stomach contents, but more frequently in the stools. Copious hemorrhage gives the stool a black, tarry appearance. Smaller quantities can be recognized by chemical and microscopic tests.

Secondary anemia is sometimes found if there has been hemorrhage, and is characterized by a decrease of red cells and hemoglobin with a low color index. Leukocytosis is common when there has been ulceration and secondary infection.

2. *Malignant Tumors.*—Malignant tumors produce essentially the same symptoms as those of a benign character when obstruction is the primary condition. More often, however, the growth is extensive, and the symptom complex of malignant growth is evident before actual obstruction sets in.

Symptoms: Pain is usually the first symptom noticed and is dull and dragging. It is fairly constant, bearing as a rule no relation to meals, but in some instances may be paroxysmal. It is commonly diffuse in the epigastrium, but may occasionally be more intense in the upper right quadrant.

Nausea is a common feature, but follows the onset of pain as a secondary complication. Vomiting is infrequent, small in amount until obstruction occurs, and has a flat taste owing to low gastric acidity. Hematemesis is common in malignant tumors, especially when erosion has taken place.

Constipation is the rule, but profuse diarrhea has been noted in cases. The history of bloody stools is a symptom to which the greatest importance should be attached. If the hemorrhage has been profuse, the patient describes the stools as tarry.

Loss of weight and cachexia are significant features of malignancy. If the loss of weight is appreciable and has taken place rapidly, it should be regarded with suspicion, since this is often one of the earliest symptoms noticed by the patient.

Malignant tumors in the second or peri-ampullary region of the duodenum sometimes cause obstruction of the ampulla. This produces biliary blockage, with subsequent jaundice that develops rapidly and is painless. Symptoms of acute pancreatitis arise as a secondary compli-

cation from the regurgitation of bile into the pancreas. These patients become rapidly and acutely ill, and the course of the disease is relatively short.

**Physical Signs:** Exquisite tenderness is rarely present, but the patient may complain of some soreness on deep palpation over the tumor. The growth may be felt through the abdominal wall if it is sufficiently large. In other instances it may be attached to surrounding structures and impart a sense of resistance on deep palpation. Distention is not marked until obstruction has occurred. Ascites may be demonstrated in some instances as a late sign and usually indicates metastases.

Gastric analysis commonly reveals low or absent free hydrochloric acid; its presence is a diagnostic finding. Free blood may be demonstrated in the gastric contents, more often in the stools, by either gross or microscopic methods.

Secondary anemia is commonly revealed by the red cell count and hemoglobin, which in late stages may reach a profound degree.

Carcinoma involving the ampulla and producing biliary obstruction gives in addition to the signs named a deep painless jaundice accompanied by intense itching. It progresses rapidly without remission. Acute pancreatitis is recognized by exquisite tenderness in the midline of the epigastrium, which is constant and progressive. If the ampulla is completely blocked, the stools are clay-colored, and chemical tests show the absence of bile pigments. The condition is practically indistinguishable from carcinoma of the head of the pancreas. It is rapidly progressive and almost uniformly fatal.

*Roentgen Observations.*—The roentgenologic picture is practically the same for benign and malignant tumors of the duodenum, and for this reason the picture for the two types is considered under one heading.

Dilatation is the easiest lesion to recognize, and denotes obstruction. It is seen on the film as a large opaque shadow roughly following the outlines of the duodenum. The edges of the shadow may be serrated, owing to the valvulae conniventes which do not disappear with dilatation. The shadow of the barium-filled stomach may overshadow the duodenum and confuse the picture. One is justified in such a case in the diagnosis of obstruction, which in the majority of instances is due to a tumor. If the obstruction is in the third portion, however, it may be confused with angioesenteric ileus. Soper regarded six hour gastric retention as strongly indicative of a tumor.

Early carcinomas producing an erosion of the duodenal wall show a filling defect resembling that of an ulcer. The defect is a small, irregular crater and is commonly found in the region of the ampulla. When supported by clinical data, it is valuable in ruling out carcinoma

of the head of the pancreas. Other types of filling defects brought about by tumors are not uncommon. Indentation into the barium shadow on both sides of the intestine is indicative of a constricting tumor. When the indentation is on one side only, the tumor is of the sessile form. Pedunculated tumors floating in the intestinal lumen produce an area of decreased density which is not attached to the wall. On rare occasions bits of barium may be caught in the crevices of a

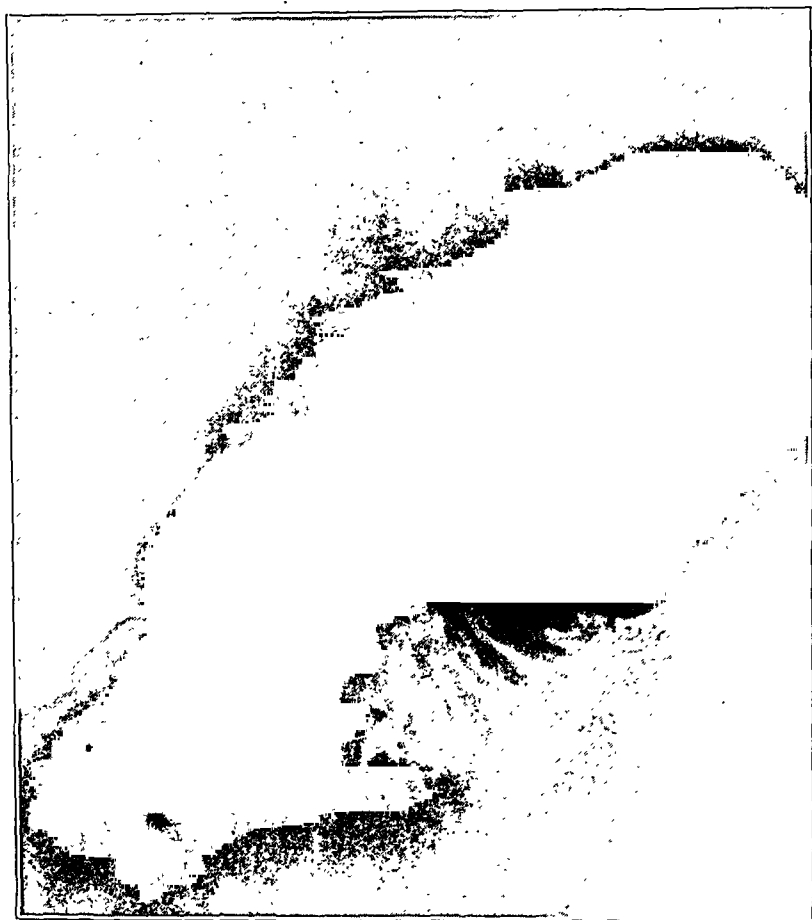


Fig. 32 (path. no. 46153, case 7.)—Roentgenogram of the stomach and duodenum following a barium meal, showing enormous dilatation. The valvulae conniventes are clearly distinguished. At operation a fibroma the size of a hen's egg was removed from the terminal third of the duodenum. The patient made an excellent recovery and has shown no recurrence of symptoms (case of Dr. Dean Lewis).

fungating papilloma and remain after the bulk of the barium has passed through the duodenum.

*Diagnosis of Duodenal Tumors.*—Carcinoma of the pylorus may simulate closely an obstructive malignant tumor of the duodenum. Symptoms appear more gradually in the former, however, and with positive roentgen observations the diagnosis is clear.

Duodenal ulcer may be a source of confusion in certain cases. Carcinomas usually produce a low, or absence of, free hydrochloric acid in contrast to the hyperacidity of the former, and the chronicity and periodicity of ulcer are lacking. Benign tumors may be very confusing, and in the absence of positive roentgen observation the diagnosis is sometimes difficult.

Tumors of the pylorus herniating into the duodenum simulate tumors of the duodenum in rare instances. They are occasionally diagnosed by means of roentgenograms, but usually pass unrecognized until operation.

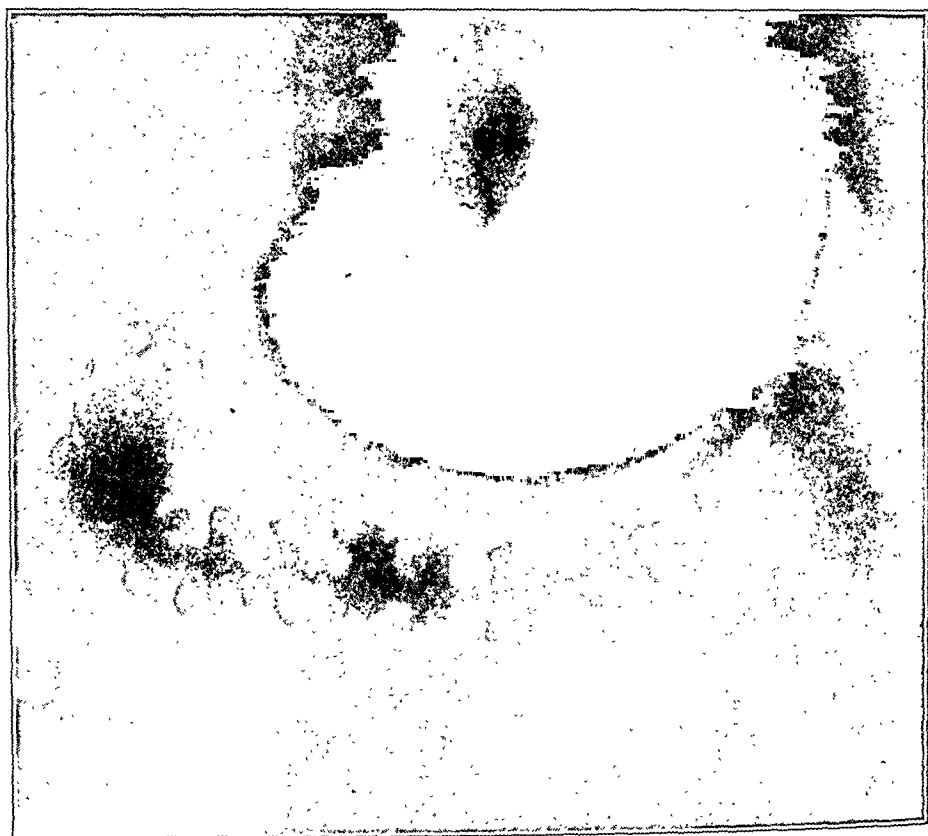


Fig. 33 (path. no. 46597).—Roentgenogram of stomach and duodenum following a barium meal and barium enema. There is a moderate dilatation of the stomach and the duodenal cap with some irregularity of the latter. There is a decrease in density of the barium shadow in the first portion of the duodenum, and the barium had not passed beyond this point. A malignant papilloma was removed from the first portion of the duodenum at operation. The patient died three days after operation from secondary infection due to contaminated catgut (patient of Dr. J. M. T. Finney).

Angiomesenteric ileus produces gastroduodenal dilatation similar to that of obstruction by tumor. The symptoms are more acute and frequently postoperative, and may be relieved by placing the patient in the Trendelenburg position.

Chronic duodenal dilatation due to constricting bands of adhesions is difficult to distinguish from obstruction due to a benign tumor. There is, however, usually a history of disease in the upper part of the abdomen or surgical intervention.

Acute gallbladder disease is sometimes considered in the diagnosis. Absence of biliary symptoms and other supporting clinical features should make the diagnosis clear.

*Prognosis.*—A favorable outcome may be expected if the tumor is benign and the technic of the operator good. The duodenum is less easily approached than other parts of the small intestine, and for this reason the success of the operation depends largely on the skill of the operator. If the tumor is malignant, the prognosis is much less favorable. If the growth has metastasized or spread to surrounding structures, temporary relief is all that can be expected. When recognized early, however, prompt surgical intervention sometimes results in complete recovery.

*Treatment.*—Surgical intervention gives the most favorable results. Early operation with excision of the tumor is usually sufficient in benign cases. Malignant tumors and lymphoblastomas necessitate the removal of a portion of intestine, with anastomosis by any of the approved methods. This may be very difficult in the duodenum if much of the intestine is removed. When the ampulla is blocked, temporary relief may be obtained by cholecystogastrostomy. Patients with inoperable malignant tumors may be helped by radium and deep roentgen treatment, but this does not result in a cure.

#### TUMORS OF THE JEJUNO-ILEUM

Symptoms of tumors in this region are mainly those of obstruction. The majority of malignant tumors and practically all of the benign group first manifest themselves in this manner. There is a small group, chiefly malignant, that does not cause obstruction, and that produces only constitutional symptoms. These tumors are most obscure and present a difficult diagnostic problem. From the symptomologic standpoint, therefore, tumors of the jejunum-ileum are grouped as obstructive and nonobstructive.

1. *Obstructive Tumors.*—Obstruction may be brought about in two different ways. The tumor may cause an intussusception or during its slow enlargement gradually encroach on the lumen. The mode of onset differs sufficiently to necessitate further subdivision.

(a) *Intussusception:* This form of obstruction occurs in 30 per cent of all tumors located in the jejunum and ileum, according to the figures of Staemmler. The incidence found in this series was slightly less, 23 per cent, the large majority being caused by benign growths. The



intussusception caused by tumors differs somewhat from that found in children in that the latter is usually spontaneous and thought to be due to a hyperactive intestine. When a tumor is present on the other hand, it is commonly assumed that the tumor is gripped by the normal peristaltic movements of the intestine and telescoped bodily by the traction thus exerted into a section lower down, the tumor always remaining at the apex of the intussuscepted piece of bowel. Spontaneous reduction is much less common than in the form occurring in children, but it may occur. The condition sometimes becomes chronic and is marked by periods of remission.

The onset of intussusception is marked by the following symptoms: A sudden, sharp, agonizing pain occurs that does not begin to abate until some hours later. It is fairly well localized, is usually in the lower part of the abdomen and occurs more commonly in the left lower quadrant. If the condition is reduced spontaneously, the pain ceases immediately. This is not likely to occur after the first twelve hours, as adhesions will have formed between the serous surfaces of the intestine.

Vomiting follows closely the onset of pain. It is repeated, but seldom becomes stercoraceous or retching. Distention and fulness develop slowly and to different degrees. These symptoms are not so marked as in some forms of obstruction, but in some instances become marked and distressing.

The patient may note the appearance of a mass in the abdomen, usually in one of the lower quadrants. This occurs some hours after the onset of the other symptoms and after the abatement of these symptoms has given him a false sense of security.

Shock is a fairly constant feature, and while it may not develop early, it is often present by the time the patient is seen by the clinician.

The bowels below the intussusception become emptied after a time. Soon after, tenesmus begins, and small amounts of bloody mucus are passed at frequent intervals, arising from the constricted end of the telescoped intestine. No further free bowel movements occur after the condition is well established.

Intussusception is marked by the following physical signs: The abdomen is slightly distended but not markedly tympanitic. In extreme cases, peristaltic waves may be visible. Tenderness is not a marked feature. Palpation of a mass is fairly constant. It is sausage-shaped, hard and rigid during the attacks of pain, and most commonly located in the region of the umbilicus. It is caused by the telescoped piece of bowel and is more easily palpable as the condition progresses.

The patient may go into a state of shock a few hours after the onset of symptoms. The skin is cold and clammy, and the patient apathetic. The pulse is rapid and thready. Respirations are rapid and shallow and the temperature frequently subnormal.

The vomitus is small in amount, thick and bile-stained. Occasionally it is fecal. Blood and mucus in small amounts comprise the bowel movements. The former is a nearly constant finding and is easily detected in the gross specimen.

(b) *Encroachment on the Lumen:* This type of obstruction is brought about by the growth of the tumor which gradually protrudes into the lumen. Benign tumors produce this encroachment by their growth within the lumen. Malignant tumors are apt to assume the constricting form and progress more rapidly. The symptoms are essentially the same, except in the cases of malignant tumors that produce anemia and cachexia.

The following symptoms are observed: The onset is gradual. The patient may feel "below par" for several months before symptoms of actual obstruction set in. Pain is the most constant single symptom. It is usually diffused over the lower part of the abdomen, but may be limited to either quadrant. It is commonly dull and aching, but may be sharp and cramplike. In either case, there is a gradual increase in the severity with few or no remissions.

Nausea and vomiting appear late. They are not marked, but fairly constant, the nausea preceding the vomiting. They recur with increasing frequency and are more severe when the obstruction is high in the intestinal tract. Distention is not oppressive, but the patient may complain of a bloated sensation after meals.

Malaise is the first symptom noticed by the patient and is more intense in malignant tumors. He feels "run down," tires easily and is generally below his standard of well-being. Anorexia may become marked, and if the patient does not force himself to eat, a serious loss of weight may ensue. Constipation is marked, but this may have been present for a number of months.

The patient seldom notices an intra-abdominal mass, unless it has reached the large size characteristic of external tumors.

The physical signs common to such a condition are: The patient is cachectic, underweight and undernourished. Emaciation may be marked, especially in cases of malignant tumors. A mass may be felt by the examiner if the tumor has reached sufficient size. In other instances, an indefinite sense of resistance is encountered. There is moderate tenderness over the region of the tumor, but this is seldom widespread unless total obstruction is present. Voluntary muscle spasm may be felt, but no actual rigidity. A slight fulness may be noticed in the early stages of obstruction, but distention and tympanites are seldom found until obstruction is complete.

Secondary anemia is the rule in malignant tumors and less common when the growth is benign. It may reach a profound degree, even to the point of endangering life when gross hemorrhages have occurred.

Obstipation is present when the obstruction is complete. When partial, constipation may alternate with diarrhea. The occurrence of blood in the stools either grossly or microscopically is a feature of significance, and this examination should never be omitted in suspected cases.

2. *Nonobstructive Tumors*.—This is a small group of tumors, chiefly malignant, which by growing externally may attain a relatively large size without causing obstructive symptoms. The tumor manifests itself



Fig. 34 (path. no. U.M. 3108).—Roentgenogram of small intestine and colon following a barium meal and barium enema. The large intestine is completely and evenly filled. The lowest coil of the ileum can be distinguished and is moderately dilated before it passes into a constricted portion just proximal to the ileocecal valve, through which a fine thread of barium can be seen entering the cecum. At operation, a large fluctuant mass was found involving the terminal ileum. It was thought to be an abscess, until biopsy of the wall showed it to be a lymphoblastoma (material obtained through courtesy of the Union Memorial Hospital).

mainly by the constitutional changes it produces and by pressure effects. The clinical picture is most obscure, and no hint of the true condition is obtained until the tumor is large enough to be felt.

Malaise is the chief symptom. The patient becomes easily fatigued and loses weight and appetite. The pulse rate may be irregular, and

he becomes short of breath on slight exertion. The gravity of the situation is not realized until the tumor is large enough to be palpated. It then is recognized as a mass that may be firmly fixed to the surrounding viscera or freely movable; it may or may not be tender. Malignant growths are hard, while certain of the benign group are soft or fluctuant.

The condition is ultimately recognized as an intra-abdominal neoplasm, but beyond this no accurate diagnosis can be made, as a non-obstructive tumor may resemble closely a neoplastic process of any abdominal viscus.

*Roentgen Observations.*—Examination of the jejunum and ileum is difficult for two reasons. It is impossible, on account of its length, to fill the small intestine completely and homogeneously with barium at one time. In the second place, if a lesion is shown in the film, the extreme mobility and the superimposed coils and loops make localization impossible.

Dilatation can be recognized, if the obstruction is marked, by a bulbous shadow on the proximal side of the tumor, past which a thin stream of the opaque substance is seen to have traveled. Filling defects are hard to demonstrate, except in the region of the ileocecal valve, where the ileum is more or less mobilized. If such a lesion is demonstrated in repeated films, it is of great value. It is in this region that the lymphoblastomas occur with greatest frequency, and the roentgenogram should be invaluable in determining the presence of a lesion. Filling defects in the terminal ileum should not be confused, however, with indentations caused by pressure from outside the intestine.

Roentgenograms of the abdomen should always be taken, since they sometimes reveal the presence of a large external tumor. In such a case, the tumor is revealed as a rather vague shadow which cannot be differentiated from other intra-abdominal masses.

*Diagnosis.*—Obstruction due to constricting adhesions may be exceedingly difficult to distinguish from that caused by neoplasms, and the clinician must rely almost solely on the history. The former usually follows some form of peritoneal irritation or surgical intervention.

Volvulus or strangulation of the intestine produces symptoms almost indistinguishable from intussusception. Distention and tympanites are more marked when adhesions are present, and no mass can be felt. Spontaneous intussusception usually occurs in children, but is clinically identical with that due to a tumor.

Appendicitis and diverticulitis have been diagnosed from the history of onset together with the clinical findings. The differentiation is especially difficult when the tumor has become necrotic. Symptoms of a tumor lack the long remissions that occur in appendicitis, and the laboratory findings are not those of an inflammatory process.

Tumors elsewhere in the gastro-intestinal tract constitute the source of greatest confusion. The symptoms as well as the physical findings are very similar. The roentgen ray is invaluable in ruling out lesions of the stomach and colon.

Neoplasms of other viscera may be confused with external growths of the small intestine, and the diagnosis is seldom made before operation.

*Prognosis.*—Benign tumors are seldom fatal if skilful surgical technic is employed in their removal. The outcome of intussusception is less favorable if the condition has existed for any length of time. Necrosis and gangrene of the telescoped intestine frequently follow, and peritonitis is not an uncommon complication. Malignant tumors give a less favorable prognosis. If recognized early and excised completely with a good margin of the intestine on either side, a cure may follow. If metastases have occurred and the glands are involved, resection does little more than prolong the course.

*Treatment.*—Early operation with complete removal of the tumor gives the most satisfactory results. Small benign growths can be excised from the intestinal wall, and the defect closed. Growths that involve much of the intestinal wall necessitate resection of part of the bowel, the amount resected depending on the extent of the growth. Patients with inoperable tumors may be temporarily improved by radium or deep roentgen treatment.

#### REPORT OF CASES

Space does not allow complete case reports of all the tumors of this series. The essential features of each case are listed in tables 9 and 10. The following cases are given for the purpose of illustrating each type of tumor. They have been selected as the most typical of the type represented and only relevant data are included.

CASE 1 (path. no. 26196; figs. 6, 8, 9 and 10).—R. W., a white man, aged 53, was admitted to St. Agnes' Hospital on May 7, 1920, complaining of periods of nausea and vomiting for the past eight months. These attacks came at intervals of three or four weeks, and had become progressively more severe and frequent. He had begun to lose weight and appetite during the last two months. Constipation was marked, and during the latter part of the disease, he felt a dull, diffuse pain throughout the lower part of the abdomen. On examination he was pallid, emaciated and cachectic. There was moderate distention of the abdomen, but no tenderness or masses could be felt. Gastric analysis showed an absence of free hydrochloric acid, and the stools were positive for occult blood. The hemoglobin was 56 per cent, and the red blood count was 2,200,000.

The condition was diagnosed carcinoma of the gastro-intestinal tract, and a laparotomy was performed on May 10, by Dr. J. C. Bloodgood. At operation, a hard constricting tumor was found midway in the jejunum. The adjacent mesenteric glands were enlarged and hard. Thirteen centimeters of the intestine were resected, and an end-to-end anastomosis performed. The patient recovered

slowly and was discharged after two months, improved. He was readmitted on December 2, with a recurrence of the original symptoms, and underwent a second operation. Metastases were found in the abdominal wall and throughout the peritoneal cavity. The condition was regarded inoperable, and the abdomen closed. He died ten days after the operation.

The gross specimen consisted of a section of small intestine containing a hard annular growth surrounding the lumen and almost entirely occluding it. The bowel was dilated above and collapsed and shrunken below the tumor. It was firm to touch, and on section was bluish white.

The microscopic section showed a tumor composed largely of hypertrophied and hyperplastic glandular tissue. This had extended in strands and nests through the submucosa and invaded the muscularis. The cells retained an alveolar arrangement, but were distorted. The cytoplasm was less abundant than in the normal epithelial cells, and the shape was cuboidal. The nuclei were large, stained lightly and showed many mitotic figures. The glands removed for biopsy showed abundant metastases of similar cells still retaining their acinar arrangement. The diagnosis was adenocarcinoma.

CASE 2 (path. no. 44558; figs. 14 and 15).—W. C., a colored man, aged 48, entered Johns Hopkins Hospital on Nov. 16, 1923, complaining of a lump in the abdomen. It was first noticed five months previously and was accompanied by a gnawing pain in the epigastrium. He had lost weight and appetite, and he complained of progressive weakness. Physical examination showed an elderly colored man, emaciated and pale, with a general glandular enlargement. An irregular mass that seemed to be continuous with the liver was felt in the upper right quadrant of the abdomen and a second larger mass on the left side, only slightly tender and relatively immovable. Examination of the stools was positive for occult blood. Other laboratory findings were essentially negative.

Inoperable carcinoma of the stomach was diagnosed, and the patient was treated palliatively. He died four weeks after admission and came to autopsy.

Examination of the abdominal viscera revealed a large rounded mass, the size of a grapefruit, in the left upper quadrant. It was in the mesentery of and attached to the jejunum. Several large metastatic nodules were found on the surface of the liver, accounting for the mass palpated on the right side. The tumor was grayish white, and on section was found to be necrotic and excavated in the center.

Microscopic section showed a densely cellular tumor composed of typical spindle cells. The cytoplasm was acidophilic and spindle-shaped. The nuclei were relatively large, oval and abundant in chromatin. The cells were densely packed in sheets and whorls, and near the outer borders of the tumor could be seen typical fibroblasts with smaller nuclei and stellate cytoplasm. Vascularity was not marked. The mucous membrane passed intact over the surface, and save for a small layer of submucosa the other structures of the wall were gone. The nodules in the liver were similar to the primary growth. The diagnosis was spindle cell sarcoma.

CASE 3 (path. no. 41291; figs. 17 and 21).—J. H., a white man, aged 47, entered the Johns Hopkins Hospital on May 5, 1927, complaining of burning and soreness in the abdomen and general malaise over a period of two months. The pain was slightly accentuated after eating, and he sometimes felt "bloated." He had lost no weight, and nausea and vomiting had not complicated the picture. Constipation had been marked, alternating at times with spells of profuse diarrhea. He was anemic looking and slightly underweight. There was

TABLE 9.—*Tumors of the Small Intestine: Symptomatic*

Path. No.	Race	Sex	Age	Location	Symptoms	Signs	Operation	Microscopic Data	Result
46597	W	M	68	Duodenum	Epigastric fulness, dull dragging pain, loss of weight; duration six months	Slight fulness, questionable mass in epigastrium to right of midline	Partial gastrectomy for fungating tumor of first portion of duodenum	Hypertrophy and hyperplasia of glandular epithelium with areas of malignancy: adenocarcinoma	Dead
46281	W	F	13	Ileum	Recurrent attacks of non-localized, cramplike pain in lower abdomen for two months	Muscle spasm, rebound tenderness, palpable mass over McBurney's point	Resection of terminal ileum; pedunculated tumor 10 cm. above ileocecal valve involving one half intestinal wall	Hyperplasia of cells arising from muscularis: myoma	Well
40153	W	M	52	Duodenum	Vomiting, epigastric discomfort, later cramplike pain, loss of weight	Marked pain, distention, succussion splash, indefinite mass 4 cm. to right of umbilicus	Excision of tumor near duodenojejunal flexure, circumscribed 6 cm. in diameter	Spindle-shaped cells of fibrous origin, fibroblasts; fibroma	Well
44950	W	F	50	Ileum	.....	.....	Resection of terminal ileum for hard, annular tumor	Large round cells of lymphoid origin, absence of reticulum: lymphoblastoma	Well
44558	O	M	48	Jejunum	Weakness, gnawing pain, loss of weight and growing mass in abdomen	Emaciation, mass in upper right quadrant continuous with liver, larger mass in upper left quadrant	Autopsy: Large irregular tumor arising from jejunal wall and extending into mesentery, metastases to liver	Closely packed spindle cells of fibrous origin, abundant mitoses; spindle cell sarcoma	Dead
44556	W	M	82	Duodenum	Sudden cramplike pain in epigastrium one day preceding death	Moderate distention, marked tenderness in upper part of abdomen	Autopsy: Marked dilatation of stomach and duodenum, ulcerated tumor obstructing duodenum in terminal portion	Malignant hypertrophy of glandular epithelium with areas of mucoid degeneration: adenocarcinoma, colloid degeneration	Dead
14221	O	F	46	Ileum	Malaise, intermittent cramp-like pain in right lower quadrant, diarrhea, nausea, vomiting for six months	Pallor, tender mass in right lower quadrant, acute obstruction six days after admission, free hydrochloric acid, 0	Resection of terminal ileum for constricting tumor just above ileocecal valve; enterocolostomy	Large, malignant round cells of lymphoid origin: lymphoblastoma	Well
44203	W	F	47	Ileum	Malaise, abdominal discomfort, meteorism, loss of weight, increasing lump in right lower quadrant	Fulness in lower part of abdomen, firm, immobile, nontender mass in right lower quadrant, emaciation	Resection of cecum, terminal ileum and ascending colon for large tumor in ileocecal region	Malignant hypertrophy and hyperplasia of glandular epithelium: adenocarcinoma	Improved
41291	W	M	47	Ileum	Burning and soreness in epigastrium, "bloating"	Pallor, firm, nontender mass to left of umbilicus, moves with respiration, free hydrochloric acid, 0	Resection of 12 in. terminal ileum for constricting tumor almost occluding lumen, extended into mesentery	Large, malignant, round cells of lymphoid type: lymphoblastoma	Dead
40322	W	F	56	Jejunum	Vomiting, eructation, fulness, constipation, loss of 35 pounds	Emaciation, pallor, sensation of resistance in left upper quadrant, no definite mass	Resection of portion of jejunal wall with lateral anastomosis; tumor involving wall, metastases in glands	Malignant hypertrophy and hyperplasia of glandular epithelium: adenocarcinoma	Dead
33264	W	F	36	Ileum	Diffuse, dragging pain in lower abdomen for five or six months	Palpable mass, nontender and immobile in right lower quadrant	Resection of 47 in. of ileum; large constricting tumor in distal portion; end-to-end anastomosis	Large, round cells of lymphoid type, mitoses abundant: lymphoblastoma	Unknown

38922	W	M	33	Small intestine	Intermittent diffuse pain in lower part of abdomen for two months	Moderate tenderness over lower part of abdomen	No report .....	Medium-sized round cells with mitoses of the lymphoid type: lymphoblastoma	Unknown
38963	W	M	6 mo.	Ileum	Intermittent vomiting and pain, six weeks; lump at umbilicus, two days	Visible and palpable tender mass to right of umbilicus; harder, immobile mass felt deeper	Reduction of double intussusception, excision of papilloma	Benign hypertrophy of glandular epithelium-forming polyp: adenoma	Well
37679	O	F	7	Ileum	Intermittent vomiting and cramplike pains localized about umbilicus, six days	Fecal vomiting, distention, tympanites, dehydration, moderate tenderness	Ileostomy and excision of papilloma from gangrenous ileum	Polyp composed of spindle cells of fibrous origin, central necrosis: fibroma	Unknown
37600	W	F	48	Ileum	No data obtainable.....	No data obtainable.....	Excision of tumor from terminal ileum found accidentally at appendectomy	Large spindle-shaped cells with plump nuclei, arising from muscle layer, mitoses abundant: myosarcoma	Dead
36506	W	F	9	Ileum	Pain in right side and mass perceptible in right lower quadrant for two weeks	Firm, slightly tender mass felt to right of umbilicus	Excision of terminal ileum and cecum for annular tumor of ileum causing ileocecal intussusception	Small, densely packed cells of lymphoid type: lymphoblastoma	Unknown
36786	W	M	49	Duodenum	Eructation, pain in epigastrium and vomiting with remissions for six weeks	Slight rigidity over right rectus muscle	Excision of small tumor nodule from anterior wall of proximal duodenum	Nests of benign cuboid cells similar to intestinal epithelium: carcinoma	Unknown
34318-1	W	F	19	Duodenum	History of anemia; blood tumor removed from tongue at 7; eructation and constipation for several years	Marked pallor, palpable spleen	Excision of small nodule from first portion of duodenum	Connective tissue hypertrophy with many blood-filled sinuses: hemangioma	Improved
2				Ileum	.....	Marked pallor, palpable spleen	Reduction of intussusception and excision of nodule from proximal ileum	Densely packed masses of small round cells resembling lymphocytes: nonspecific granuloma (lymphoblastoma)	Improved
31805	..	..	..	Small intestine	No data obtainable.....	No data obtainable.....	Resection of a 3 cm. nodule from wall of intestine; metastases to glands	Large malignant epithelial cells in sheets: medullary carcinoma	Dead
30454	W	M	48	Jejunum	Tenderness in epigastrium, loss of 23 pounds, rectal bleeding	Moderate tenderness, palpable mass in left upper quadrant	Resection of duodenojejunal flexure for large tumor 5 cm. below flexure	Malignant hypertrophy and hyperplasia of glandular epithelium: adenocarcinoma	Dead
28561	O	M	68	Ileum	Anorexia, diffuse cramplike pains, vomiting, lump in right lower quadrant increasing for six months	Emaciation, pallor, sausage-shaped mass in right lower quadrant, occasional peristaltic waves	Resection of terminal ileum for intussusception caused by a hard, constricting tumor 8 in. above ileocecal valve	Malignant hypertrophy and hyperplasia of glandular epithelium: adenocarcinoma	Dead
27187	O	M	18	Ileum	Acute generalized pain after straining twenty-four hours previously, vomiting and weakness	Movable, slightly tender mass in right lower quadrant	Resection of 2 ft. of ileum for gangrenous intussusception due to two sessile tumors	Medium-sized round cells similar to lymphocytes, hyperchromatic nuclei: lymphoblastoma	Well
26106	W	M	53	Jejunum	Nausea, vomiting, anorexia, weakness, diffuse abdominal pain, intermittent, eight months	Emaciation, dull tenderness most marked around umbilicus	Resection of 13 in. of jejunum for hard constricting tumor metastasizing to glands	Malignant hypertrophy and hyperplasia of glandular epithelium: adenocarcinoma	Dead



TABLE 9.—*Tumors of the Small Intestine: Symptomatic—Continued*

Path. No.	Race	Sex	Age	Location	Symptoms	Signs	Operation	Microscopic Data	Result
26163	W	M	5	Ileum	No data obtainable.....	No data obtainable.....	Resection of portion of ileum for hard constricting tumor; lateral anastomosis	Large round cells of the lymphoid type densely packed together, mitotic figures: lymphoblastoma	Well
24671	W	M	6	Ileum	Diffuse cramplike pains, vomiting, melena, palpable mass; symptoms intermittent, four weeks	Protruding sausage-shaped mass to left of umbilicus; exophthalmus, left	Partial resection of ileum for intussusception caused by hard constricting tumor; recurrence	Densely packed round cells of the lymphoid series, mitoses and metastases: lymphoblastoma	Well
24870	O	M	60	Ileum	Constipation, anorexia, loss of weight; later vomiting, epigastric pain, hematemesis	Pallor, emaciation, peristaltic waves, indefinite sense of resistance in mid-epigastrium	Excision of bloody pedunculated tumor of ileum including lumen; glands enlarged	Fungating tumor composed of tremendous hypertrophy of blood vessels, round cell infiltration: hemangioma, simple	Well
18427	W	M	39	Ileum	Constipation, nausea, vomiting, abdominal cramps, blood-streaked stools, loss of weight	Pallor, emaciation, firm, round, nontender, movable mass to right of umbilicus	Resection of cecum and terminal ileum for ileocecal intussusception caused by hard, annular tumor of ileum	Dense packed round cells of lymphoid type, no mitoses: lymphoblastoma	Well
10485a	O	M	24	Ileum	Symptoms of acute intestinal obstruction; no further data available	Signs of acute intestinal obstruction; no further data available	Resection of three separate portions of ileum for three intussusceptions caused by papillomas; ten tumors in all	Densely packed large round cells of lymphoid series, mitotic figures abundant: lymphoblastoma	Well
10485b	O	M	30	Jejunum	Symptoms of chronic high intestinal obstruction; no further data obtainable	Signs of chronic high intestinal obstruction; no further data obtainable	Resection of portion of jejunum for papilloma causing obstruction and duodenal dilatation	Small cells arranged in acinar formation and resembling normal pancreatic tissue: accessory pancreas	Dead
13047	W	M	35	small intestine	Malaise, cachexia; perceptible tumor in abdomen for six months	Moderate tenderness in epigastrium, palpable tumor to left of umbilicus	Resection of part of small intestine for hard annular tumor causing partial obstruction; metastases to glands	Malignant hypertrophy and hyperplasia of glandular epithelium: adenocarcinoma	Dead
10599	W	F	11	Jejunum	Intermittent attacks of cramplike pain, nausea and vomiting for three years	Pallor, intestinal patterns, emaciation, epigastric fullness, fixed, nontender mass to left of umbilicus	Enterostomy and excision of portion of upper jejunum for multiple polyps causing chronic intussusception	Moderate glandular hypertrophy in a vascular stroma, no malignancy: adenoma	Well
7489	W	M	24	Ileum	Anorexia, nausea and vomiting, diffuse cramping pain, malaise and loss of weight for eight months	Pallor, intestinal patterns, large, hard, tender, sausage-shaped mass in epigastrium moving with respiration	Resection of 17 cm. of ileum for multiple hard pedunculated tumors causing chronic intussusception	Hypertrophied and dilated glandular structure without malignancy: adenoma	Improved
6509	W	M	33	Duodenum	No data obtainable.....	No data obtainable.....	Resection of small hard tumor of the duodenum	Hypertrophied and hyperplastic glandular epithelium with mitoses: adenocarcinoma	Unknown

G6223	C	F	64	Duodenum	Malaise, anorexia, itching, loss of weight and painless jaundice for six months	Marked jaundice, enlarged liver, indolent sense of resistance in epigastrium	Autopsy: Ulcerated and indurated area about antrum 1.5 cm. in diameter	Malignant hyperplasia of glandular epithelium; adenocarcinoma	Dead
G6310	W	M	54	Duodenum	Epigastric fulness, eructation and pain with jaundice; loss of weight	General pallor, scleroid tint, moderate distention	Autopsy: Large indurated mass in region of antrum involving head of pancreas	Hyperplasia of glandular epithelium and hyperadenocarcinoma	Dead
G7003	W	M	56	Ileum	Intermittent attacks of dull pain, vomiting and distention for nine months	Emaciation, acute distention, large mass in either lower quadrant	Autopsy: Large tumor mass in ileum 60 cm. above ileocecal valve causing partial obstruction	Densely packed large round cells showing mitoses; lymphoblastoma	Dead
G6316	W	M	37	Ileum	Nausea, vomiting, headaches, loss of vision, falling memory, mental deterioration	Essentially negative except for neurologic signs indicating frontal lobe tumor	Autopsy: Multiple small sessile tumors in upper jejunum, hard bases, some ulcerated; secondary nodules in brain	Densely packed masses of staining nuclei showing mitoses, metastases to brain; lymphoblastoma	Dead
G2400	W	M	57	Ileum	Diffuse epigastric pain and fulness, nausea and vomiting, diarrhea, intermittent for seventeen years; worse for past two years; worse prostration for one year; severe one month before admission	Voluntary rigidity, transverse ridge above umbilicus moving with respiration	Autopsy: Multiple polyps in lower ileum, inflammation and obliteration of normal structure, ulcerative colitis	Benign hyperplasia and hyperplasia of glandular epithelium; adenomas, multiple	Dead
G1842	W	M	17	Ileum	Constipation, pain in epigastrium and palpable mass above umbilicus for three months	Slight fulness in epigastrium, no masses but a doughy feeling to palpation	Autopsy: Firm thickening in ileum 60 cm. above valve, ulcerated; second tumor 60 cm. above this	Abundance of large round cells of lymphoid type, vesicular nuclei; lymphoblastoma	Dead
G1700	C	M	35	Ileum	Epigastric pain, fulness and eructation, worse after meals; duration six days	Abdominal distention, large, hard, irregular tumor between symphysis and umbilicus, nonmovable and tender	Autopsy: Large, hard, nodular tumor of lower ileum involving glands, ulceration of mucous membrane	Densely packed large round cells of lymphoid series; lymphoblastoma	Dead
G1100	W	F	54	Duodenum	Swelling of abdomen, epigastric pain, diarrhea, loss of weight; duration six months	Dependent edema, abdominal distention, fluid wave	Autopsy: Dilatation of ileum above obstructing polyp, generalized peritonitis	Inflammatory reaction surrounding old ulcer, forming glandular hypertrophy	Dead
G662	W	F	45	Duodenum	Fatness vomiting, epigastric pain, three months; paroxysmal pain, three days	Emaciation, exquisite pain in epigastrium to left of midline	Autopsy: Hard irregular third of duodenum, no obstruction	Malignant hyperplasia of glandular epithelium; adenocarcinoma	Dead
G223	W	M	27	Ileum	Diarrhea, vomiting, painful urination, four months	Ileumatemesia, epigastric pain in epigastrium to left of midline	Autopsy: Two perforated ulcers in first third of duodenum, hard indurated bases; generalized peritonitis	Malignant hyperplasia of glandular epithelium; adenocarcinoma	Dead
UM	W	M	69	Ileum	Malaise, indigestion, irregular pulse, three weeks	Emaciation, pallor, tympanites, dull pain to pressure in epigastrium	Autopsy: Three tumors arising from wall of lower ileum causing partial obstruction	Densely packed round cells of lymphoid type, numerous mitoses; lymphoblastoma	Dead
						Incision and drainage of large abscess attached to ileum	Section of wall of abscess showed densely packed large round cells of lymphoid type with abundant mitoses; lymphoblastoma		Dead

TABLE 10.—*Tumors of the Small Intestine: Asymptomatic*

Path. No.	Race	Sex	Age	Location	Clinical Condition	Gross Pathologic Data	Microscopic Pathologic Data	Result
G10745	W	M	41	Jejunum	Coronary sclerosis	Nodule 2.5 cm. in diameter, pushing externally in upper portion of jejunum	Cuboid cells with small nuclei arranged in acini resembling normal pancreatic tissue; aberrant pancreatic tissue	Dead
G11699	W	M	52	Ileum	Ulcerative colitis .....	Soft nodule lifting mucosa in midportion of ileum, freely movable	Cuboid cells resembling normal pancreatic tissue; islands of Langerhans and dilated ducts; aberrant pancreatic tissue	Dead
G10613	C	F	40	Duodenum	Acute yellow atrophy of liver	Soft grayish nodule 7 mm. in diameter attached to anterior wall of duodenum in terminal portion	Tissue resembled normal pancreas, cells arranged in acini; aberrant pancreatic tissue	Dead
G10584	W	M	68	Ileum	Benign prostatic hypertrophy	Oval, rubbery mass 6 mm. in diameter in upper portion of ileum	Tissue composed of hypertrophied cells of muscle origin; spindle-shaped cells, oval nuclei; myoma	Dead
G10579	C	F	7	Jejunum	Rheumatic endocarditis .....	Firm nodule 5 mm. in diameter located 25 cm. below flexure, grayish pink on section	Irregular, sharply delineated lobules of cuboid cells in acinar arrangement; resembled pancreas; aberrant pancreatic tissue	Dead
G10569	W	M	77	Small intestine	Myocardial failure, coronary infarcts	Multiple small reddish nodules in wall of small intestine 1 to 5 mm. in diameter, less frequent toward ileocecal valve	Tumors made up largely of blood extravasations; connective tissue stroma and white fibrous centers in some; hematomas	Dead
G10220	W	M	41	Duodenum	Acquired hemolytic jaundice..	Small nodule 6 mm. in diameter in terminal third of duodenum	Large cuboid cells with small nuclei in acinar arrangement; resembled pancreatic tissue; aberrant pancreatic tissue	Dead
G10140	W	M	77	Ileum	Benign prostatic hypertrophy	External tumor of ileum 10 cm. above ileocecal valve 2 cm. in diameter, grayish color on section	Densely packed large round cells of lymphoid series showing many chromatin particles in nuclei; lymphoblastoma	Dead
G10048	..	..	..	Ileum	Carcinoma of lung.....	Tumor nodule 1.5 cm. in diameter projecting into lumen of ileum 8 cm. above ileocecal valve	Epithelial cells of columnar type growing in strands and acini; did not look malignant, but metastases were found in liver and lymph nodes; argentaffin or carcinoid tumor	Dead
G10023	C	F	44	Ileum	Appendicitis and general peritonitis	Small polyp near midportion of ileum composed of a cluster of encapsulated nodules	Epithelioid cells arranged in strands and sheets embedded in fibrous vascular stroma; encapsulated; argentaffin or carcinoid tumor	Dead
G 9810	W	M	78	Ileum	Benign prostatic hypertrophy and bronchopneumonia	Dark red semispheroid tumor partially occluding lumen 1 meter above valve	Old blood clot continuous with thrombosis of mesenteric vein; hematoma	Dead
G 8875	W	M	62	Ileum	Fracture of femur, postoperative gastric hemorrhage	Lemon-colored spheroid nodule 5 cm. in diameter, projecting into lumen 90 cm. above valve	Irregular masses of epithelioid cells supported by connective tissue stroma; cells encapsulated; argentaffin or carcinoid tumor	Dead
G 7492	W	M	12	Small intestine	Postoperative laryngeal stricture	Irregular thickenings throughout small intestine forming projecting lumps into the lumen	Dense collections of small round cells of the lymphoid type showing no evidence of malignancy; lymphoblastoma	Dead
G 7374	W	M	72	Jejunum	Benign prostatic hypertrophy	Soft pedunculated yellow tumor hanging loosely from wall of jejunum in upper portion, covered entirely by mucosa	Large fatty cells supported by scanty connective tissue stroma; lipoma	Dead
G 7353	W	M	77	Ileum	Carcinoma of bladder.....	Soft, oval, polypoid tumor 1.5 cm. in diameter, attached by fine pedicle to wall of ileum 25 cm. above valve	Large epithelioid cells in irregular acinar formation, limiting membrane; no evidence of malignancy; argentaffin or carcinoid tumor	Dead
G 6739	C	M	50	Jejunum	Carcinoma of stomach.....	Small circumscribed tumor 5 mm. in diameter, in jejunal wall projecting into lumen, different from tumor in stomach	Benign hypertrophy of glandular epithelium extending through submucosa; adenoma	Dead
G 6480	W	F	53	Ileum	Adenocarcinoma of thyroid..	Small button-like projection under mucosa of ileum	Tumor composed entirely of large fat cells; scant fibrous supporting tissue; lipoma	Dead
G 6378	W	M	63	Ileum	Carcinoma of liver.....	Small, soft tumor nodule embedded in wall of ileum 1 meter above ileocecal valve		

G 5465	W	M	64	Duodenum	Myocardial failure	Bean-shaped nodule embedded in mucosa of duodenum near ampulla	Large fat cells supported by scanty connective tissue stroma: lipoma	Dead
G 5464	W	F	62	Duodenum	Pneumonia, myocarditis	Two small polypoid growths arising from wall of duodenum near ampulla	Benign hypertrophy of glands of mucosa; no malignancy: adenoma	Dead
G 4729	W	F	42	Duodenum	Pneumonia	Stony hard, nodular elevation of duodenal wall opposite elevation of duodenum just below pylorus, mucosa intact	Densely packed masses of glands with pyknotic nuclei: lymphoblastoma	Dead
G 4693	C	M	2 d	Duodenum	Cerebral hemorrhage	Small, elevated nodule in wall of duodenum just below pylorus, mucosa intact	Irregular cystic structure lined by tall columnar epithelium and containing amber fluid: cyst	Dead
G 4110	C	F	66	Ileum	Aortic aneurysm	Firm, wart-like tumor 1 cm. in diameter 10 ft. above iliocecal valve	Sharply limited groups of cuboid, epithelioid cells in acinar formation; no malignancy: argentaffin or carcinoid tumor	Dead
G 3873	W	M	60	Ileum	Syphilitic aortitis	Small, rounded submucous nodule in lower part of ileum	Nests of cuboid cells with definite limiting membrane; no malignancy: argentaffin or carcinoid tumor	Dead
G 3872	W	F	34	Duodenum	Puerperal infection and peritonitis	Circumscribed tumor the size of a hazelnut in distal third of duodenum	No carcinoid tumor	Dead
G 3496	C	M	38	Ileum	Tetanus	Few small rounded nodules 1 to 5 mm. in diameter near middle of ileum	Benign hypertrophy of glandular epithelium: adenoma	Dead
G 3385	W	M	23	Jejunum	Myocardial failure	Subserous nodule 6 mm. in diameter just below flexure	Benign hypertrophy of spindle-shaped cells of origin, oval nuclei, myoma	Dead
G 3178	C	F	30	Ileum	Brain tumor	Serous sessile polyps from 5 to 8 mm. in diameter in first third of duodenum	No sections; diagnosis: fibroma (from previous report)	Dead
G 3102	C	M	60	Jejunum	Puerperal infection	Several closely set filiform polyps in lower ileum	Polyps composed of germinal centers surrounded by hypertrophied glandular epithelium: adenoma	Dead
G 2762	C	M	52	Jejunum	Pneumonia, myocarditis	External tumor of jejunum 1.5 cm. in diameter attached to serous coat by pedicle	Hyaline degeneration of spindle-shaped cells of muscle origin: myoma	Dead
G 2756	W	M	70	Ileum	Carcinoma of rectum	Three opaque, grayish nodules in jejunum 2 to 3 mm. in diameter contained whitish fluid	Cystic structure, sacs lined by endothelium and separated by delicate septums: lymphadenoma	Dead
G 2513	W	M	54	Jejunum	Chronic nephritis and pyelitis	Firm nodule, 2.5 by 2 by 1 cm., near mesenteric attachment in midportion of ileum	Large fatty cells separated by delicate connective tissue stroma: lipoma	Dead
G 2198	C	M	52	Ileum	Bronchopneumonia	Numerous small hemorrhagic nodules 3 to 8 mm. in diameter along course of veins in jejunum	Tumor composed of large sinuses filled with old blood and infiltrated with leukocytes: cavernous hemangioma	Dead
G 1701	C	M	35	Ileum	Endocarditis	Six nodules 3 to 7 mm. in diameter in upper ileum, covered by normal mucous tissue	Malignant change in epithelial cells of mucosa with hypertrophy: adenocarcinoma	Dead
G 1601	C	M	61	Ileum	Nephritis and pericarditis	Numerous filiform polyps in lower ileum projecting above mucosa	Benign hypertrophy of glandular epithelium of mucosa around germinal centers: adenomas	Dead
G 1520	C	M	42	Ileum	Bronchopneumonia	Small external subserous nodule in midportion of ileum	Tumor composed of spindle cells of fibrous tissue and mature fibroblasts: fibroma	Dead
G 1018	W	F	20	Duodenum	Myocardial failure	Finger-shaped elevation 1 by 4 cm. in upper ileum parallel to lumen	Benign hypertrophy of glandular epithelium supported by dense connective tissue: adenoma	Dead
G 443	C	M	..	Jejunum	Chronic nephritis	Three or four small polypoid projections into lumen scattered along duodenum	Hypertrophy of glands of mucosa; occasional cystic mucous-filled areas: adenothelium: adenocarcinoma	Dead
G 367	W	F	52	Ileum	Tuberculosis	Nodule in lower jejunum the size of a split pea, hard and nonmovable	Malignant hypertrophy of glandular epithelium largely of the mucous cell type: adenoma	Dead
G 226	W	M	24	Duodenum	Carcinoma of gallbladder	Mucous polyp in upper ileum the size of a pea, soft and movable	Benign hypertrophy of glandular epithelium: adenoma	Dead
G 15	O	M	38	Duodenum	Chronic nephritis	Sessile tumor the size of a bean beneath the mucosa in the second part of the duodenum, freely movable	Large fat cells separated by delicate connective tissue stroma: lipoma	Dead
						Soft, yellow, submucous tumor the size of a bean in first part of the duodenum		

moderate tenderness on deep palpation just above the umbilicus, and in this region could be felt a tumor approximately the size of a lemon. The examiner could not be certain of its attachment. Laboratory tests were negative, except for a mild secondary anemia.

The condition was diagnosed carcinoma, and the location of the tumor was undetermined. An exploratory laparotomy was performed on May 7, by Dr. J. M. T. Finney. A tumor was found almost occluding the lumen of the ileum near the midportion. It was smooth and lobulated. It was removed, together with 13 inches of the ileum. There were cordlike extensions through the lymphatics to the mesenteric lymph nodes, which were slightly enlarged. The patient recovered from the operation rapidly and was discharged from the hospital improved. Shortly after discharge, however, the symptoms recurred, and the course was rapidly downhill. He died three months after operation. Autopsy was not done.

The gross specimen consisted of a smooth, rounded tumor, the size of an orange, completely surrounding the ileum. When sectioned, the tumor proved to be dilated in the center, forming a hollow sphere lined by the intact mucosa. The walls of the tumor were about 1 cm. thick and constricted the lumen at points of entrance and exit.

The microscopic section showed densely packed masses of large round cells resembling those of the lymphoid series. Some of the cells were small, with scanty cytoplasm and a small dark nucleus. Others were much larger, and the nucleus stained very light, with, however, many chromatin particles. Between these two types could be seen variant cells of all grades. There was an admixture of leukocytes, chiefly of the neutrophilic type, but with a few eosinophils. Occasional giant cells could be seen. The stroma consisted of fine strands of connective tissue. Vascularity was not marked, but throughout the tumor could be seen small capillaries. The mucosa had remained intact, but the tumor had invaded all the layers of the intestinal wall to the serosal surface. The diagnosis was lymphoblastoma of the malignant lymphocytoma type.

CASE 4 (path. no. 44221).—A. P., a colored woman, aged 46, entered the medical service of the Johns Hopkins Hospital on Oct. 16, 1928, complaining of general malaise, anorexia and loss of weight over a period of six months. Intermittent cramplike pains began three months before admission, and were accompanied by profuse diarrhea seven or eight times a day. The pain was at first localized to the epigastrium, but it later radiated over the entire abdomen, and at the time of admission was most severe in the right lower quadrant. The patient showed an appreciable loss of weight and pallor of the mucous membranes. In the right lower quadrant, an irregular mass could be felt, the size of a tangerine. It was moderately tender, and there was some muscular rigidity over the area. The same mass could be made out on rectal examination. Roentgenograms of the gastro-intestinal tract showed the colon incompletely filled. Tests of the stools for occult blood were positive. The hemoglobin was 72 per cent. There was no free hydrochloric acid in the gastric contents. The condition was diagnosed as chronic intestinal obstruction, and the patient was transferred to the surgical service for laparotomy.

The operation was performed on October 29, by Dr. Dean Lewis. An area of thickening and induration was found in the lower part of the ileum which had partially constricted the lumen of the intestine. No definite tumor formation was made out, but the condition was thought to be an early stage malignant change. The area was removed, together with 13 cm. of normal intestine, and an enterocolostomy performed. When the intestine was opened after removal of the area the wall was thickened, the mucosa ulcerated and two or three nodular projections were found pointing toward the lumen.

The patient recovered from the operation rapidly and was discharged from the hospital improved on November 17. She had no further symptoms until December, 1930, when she noticed the presence of a tender gland beneath the angle of the right side of the jaw. This grew rapidly for about ten days and was somewhat tender, then ceased to grow and became nontender. She lost weight, became weak and tired easily. She returned to the hospital in February, and a gland as large as an English walnut was found beneath the right side of the jaw. It was firm, movable and not tender. Results of physical examination were otherwise negative. The gland was excised for diagnosis. She recovered from the operation and was discharged on February 18. Since that time the general symptoms have decreased. A roentgenogram of the chest was negative.

The section of intestine removed has been described. The gland removed at the final operation was smooth and discrete. The microscopic examination of the intestinal tumor showed an infiltrating tumor growth extending beneath the mucosa for a depth of from 3 to 5 mm. The mucosa was eroded over the area. The cellular structure comprised a dense homogeneous mass of round and polyhedral cells, which had grown chiefly in the submucosa, but had also extended into the muscular layer. The cells resembled those of the lymphoid series. The largest were polyhedral with small amounts of cytoplasm in stellate or concentric shape. The smaller cells were found near the advancing edges of the tumor, and closely resembled normal lymphocytes. There was an abundance of reticulum scattered throughout the tumor. A section from the gland in the neck showed it to be similar in every way.

This case was important in view of the recurrence. No evidence of metastasis to glands or organs was found at the first operation. The similarity of the gland removed from the neck proved its origin from the initial lesion. The malignant cells had apparently been quiescent for a period of more than two years, then appeared in the neck. Although there is no evidence of another seat of tumor growth at the present time, the patient no doubt harbors other cells of the same type in the body, which will sooner or later bring about a recurrence with exitus.

CASE 5 (path. no. 38963; fig. 22).—K. W., a 7 month old white boy was brought to the Johns Hopkins Hospital on March 27, 1926, with the complaint of intermittent attacks of pain and vomiting over a period of six weeks. During the attacks, three in number, the child would draw up its legs and cry, seemingly in agonizing pain. Vomiting would follow shortly, and he would be relieved for a short time. This occurred frequently during each attack, which lasted from two days to a week. The last attack began a week before admission and continued unabated, becoming more severe on the day of admission. On this day the parents noticed the appearance of a tubular-shaped mass in the abdomen. Physical examination showed an undernourished infant, evidently in great pain. The abdomen was not rigid, but a tubular, sausage-shaped mass could be felt just to the right of the umbilicus. The bowel movements consisted of frequent small amounts of bloody mucus. Laboratory findings were negative.

The diagnosis of acute intussusception was made, and the abdomen opened. A circular intussusception was found in the ileum about 2 feet above the ileocecal valve, with a small papilloma at the apex. This was reduced, and the papilloma excised. The patient made an uneventful recovery and was discharged from the hospital well on April 7.

The gross specimen consisted of a polyp 2.5 by 1 cm. The mucosa covered it entirely, but was eroded on one side. It was reddish brown and elastic. The cut section showed a firm yellowish-white center surrounded by a spongy red border.

Microscopic examination showed the tumor to be composed of two elements. The center was typical fibrous tissue that was continuous with the stalk. Throughout this fibrous center, especially near the outer edges of the tumor, was a cellular infiltration consisting chiefly of small round cells and leukocytes. Surrounding this area was a thick border of hypertrophied mucous membrane. Throughout the glandular hyperplasia, the cells regained their columnar form with the nuclei grouped at the bottom of the slender cytoplasm. Between the glandular elements there was a dense infiltration of leukocytes and red cells, and in one portion the mucous membrane was necrotic. The glandular hypertrophy extended into the fibrous center, in some places forming nests of mucosal epithelium, which resembled the normal glands of the membrane. The diagnosis was benign adenoma.

CASE 6 (path. no. 10584; figs. 4 and 23).—L. G., a white man, aged 68, was admitted to the Johns Hopkins Hospital, complaining of marked frequency and nocturia with difficulty of retention over a period of six months. There had been gross hematuria on one occasion. Results of the physical examination were negative, except for enlargement of the prostate. A vesical calculus was found on cystoscopic examination. A prostatectomy was advised and performed, but the patient died of postoperative pneumonia and came to autopsy.

Postmortem examination confirmed the clinical urologic impression. In routine examination of the viscera, a small submucous nodule was found in the first portion of the ileum. It was oval, movable, rubbery and hard in consistency. On section, this nodule had the striped appearance of a myoma of the uterus.

The microscopic section showed a tumor composed of hypertrophied muscle fibers arising from the circular coat of the muscularis. The cells were spindle-shaped and stained well with the eosin stain. The nuclei were rather large and plump and stained lightly. No mitotic figures could be seen. Very little stroma was present. The tumor was limited by a definite fibrous capsule which it made no attempt to invade. The diagnosis was myoma.

CASE 7 (path. no. 46153; figs. 25 and 32).—E. L., a white man, aged 52, came to the Johns Hopkins Hospital on Oct. 29, 1929, complaining of recurrent nausea and vomiting over a period of three months. The attacks lasted several hours, during which he vomited every hour or two, the vomitus being profuse and bile-stained. Pain was not a marked feature. Toward the latter part of his illness he had some distention and epigastric distress. On the day of admission, however, he had several cramplike attacks of pain. Loss of weight had been marked. When first seen after admission, the patient was in agony. The legs were drawn up to the body, and he vomited large amounts of bile-stained fluid frequently. There was marked tenderness in the epigastrium and moderate distention. Occasional peristaltic waves were visible, and a succussion splash was elicited. An indefinite mass was felt just to the left of the umbilicus. Roentgenograms made after a barium meal showed marked dilatation of the stomach and duodenum, with the point of obstruction near the duodenojejunal flexure. The diagnosis was tumor of the duodenum, and a laparotomy was performed by Dr. Dean Lewis on October 31.

When the abdomen was opened, a large circumscribed tumor was found attached to the duodenum in its distal third. It projected into the lumen and was covered by a freely movable, intact mucosa. The tumor was excised, together with a part of the duodenal wall, and the opening was closed. The patient made an uneventful recovery and was discharged two weeks after operation; he reported for reexamination sixteen months later in good health.

The gross specimen consisted of a firm encapsulated tumor 9.5 by 5 by 4 cm. It was incorporated in the wall of the intestine. It was grayish white and fibrous. Cut section showed the tumor homogeneous throughout, except for a softer portion of beginning degeneration just beneath the mucous membrane.

Microscopic examination showed a tumor composed almost entirely of connective tissue, arising apparently from the submucosa. The cells were spindle-shaped with abundant light-staining cytoplasm in wavy strands. The nuclei were small, dark and oval. Fibroblasts could be seen, being more numerous near the outer edges of the tumor. The soft area noted in the gross specimen was composed of a mass of degenerated cells and necrotic material. Vascularity was not marked, although several small vessels were scattered throughout. The diagnosis was fibroma.

CASE 8 (path. no. 6739; fig. 26).—J. P., a colored man, aged 50, was admitted to the Johns Hopkins Hospital, complaining of a progressive sensation of fulness in the abdomen for one year. Symptoms of obstruction developed toward the end. He had lost 20 pounds (9 Kg.) in weight. Physical examination showed typical signs of obstruction of the pylorus, epigastric distention, frequent vomiting and inability to retain food. A slightly tender mass was palpated in the epigastrium. There was no free hydrochloric acid in the gastric contents, and carcinoma of the stomach was diagnosed.

A laparotomy was performed, and the clinical diagnosis confirmed, but the condition was inoperable. The postoperative course was progressively downhill, and the patient died from pneumonia on the tenth day.

At autopsy, the tumor was found to occupy the lesser curvature of the stomach and had invaded the pylorus. Metastases to the liver and lymph glands had occurred. A small submucous nodule was found in the jejunum during routine examination of the intestines. It was about 5 mm. in diameter. The tumor was not attached to the mucosa which had eroded over it. The tumor was yellow-gray, fairly soft and definitely circumscribed.

Microscopic examination proved immediately that this nodule was different from the one in the stomach. It was composed of more or less discrete nests of cells that were infiltrative rather than invasive. The cells were round, oval or cuboidal, the former type being found nearest the center of the nest. In some portions, they were flattened by pressure and almost spindle-shaped. The nuclei were round or oval, corresponding roughly to the general shape of the cell. They stained darkly, and were rich in chromatin. They did not, however, show the mitotic figures of malignant change. The cytoplasm was granular and moderate in amount. The cell nests were supported in a stroma of dense fibrous tissue. Vascularity was not marked, but occasional small vessels could be seen in the groups of cells. The diagnosis was argentaffin tumor.

CASE 9 (path. no. 16485; fig. 20).—S. W., a colored man, aged 24, was admitted to the hospital, complaining of acute abdominal pain of twenty-four hours' duration. He had vomited several times, each time a small amount of thin, watery, bile-stained vomitus. He had had but one bowel movement, and a dose of castor oil had not caused a movement, but rather had accentuated the pain. Physical examination revealed a young Negro, evidently in acute distress. He was in a mild state of shock, with cold, clammy skin, rapid pulse and shallow respirations. The abdomen was not markedly tender, but was moderately distended and tympanitic. Acute obstruction was diagnosed, and the abdomen was opened by Dr. G. J. Winthrop. An intussusception was found in the middle portion of the jejunum about 6 inches (15 cm.) in length. Adhesions had formed between the serous surfaces of the telescoped intestine and prevented reduction. The



intussusception was then excised, and a lateral anastomosis performed. The patient recovered from the immediate effects of the operation and seemed completely well. On the day before leaving the hospital, however, he suddenly died without any untoward symptoms. Autopsy showed a pulmonary embolus as the cause of death.

The gross specimen removed at operation consisted of a piece of small intestine 1 foot (30.48 cm.) in length. A small, papillomatous tumor the size of a hazelnut was found at the apex of the intussusception. It was red and hyperemic. The mucous membrane was intact and freely movable over the entire tumor. It was attached to the intestinal wall by a short thick pedicle. Cut section was gray near the center and reddish gray at the border. The consistency was soft and spongy.

The microscopic section was interesting. With the naked eye, certain masses of angular, lobulated shape could be seen. These stained much darker than the surrounding tissue. Under the microscope these lobules resembled closely the tissue of the normal pancreas. The cells were relatively uniform in size and in a definite alveolar arrangement. The cytoplasm was basophilic and contained zymogen granules. The nuclei were round or oval, located at the bases of the pyramidal-shaped cells. They stained dark and were rich in chromatin. Typical islands of Langerhans could be seen containing the two characteristic types of cells through which an occasional capillary ran. The stroma was composed of a dense fibrous tissue which separated the lobules. Occasional large dilated ducts could be seen in the stroma lined by short columnar epithelium. The tumor was circumscribed, and its origin could be traced to the submucosa. The diagnosis was aberrant pancreatic tissue. (This was a patient of Dr. G. J. Winthrop, Mobile, Ala.)

CASE 10.—(path. no. 24867; fig. 29).—E. B., a colored man, aged 60, entered the Johns Hopkins Hospital on July 28, 1919, with the complaint of anorexia and loss of weight. The symptoms had developed over a period of six months. Pain was not a constant feature, but had been present in attacks, always worse after eating. He had vomited several times, and on two occasions there had been gross blood in the vomitus. Constipation was marked. He had grown much worse during the two weeks previous to admission, and had been practically unable to retain any food. Loss of weight had been marked, and the epigastric pain was more severe. The patient was emaciated with marked pallor of the mucous membranes. There was moderate distention, and active peristaltic waves could be seen coursing frequently over the entire abdomen. Just above the umbilicus, an indefinite sense of resistance could be made out. Tests of the stools were negative for blood. Roentgenograms taken after a barium meal showed enormous dilatation of the small intestine, but the point of obstruction could not be determined. There was a moderate secondary anemia. Intestinal obstruction of unknown etiology was diagnosed, and the patient was transferred to the surgical service for laparotomy.

The abdomen was opened on Aug. 5, 1921, by Dr. Mont Reid, and a tumor the size of an English walnut found in the ileum 4 feet (121.92 cm.) above the ileocecal valve. It was sessile in form and almost completely occluded the lumen. The mucous membrane was intact over the tumor, but rather firmly attached. It was reddish brown and soft to the touch. On section, it was red throughout, and blood could be squeezed from it. The mesenteric glands were enlarged but soft. The tumor, together with 6 inches (15.24 cm.) of the ileum, was excised, and an end-to-end anastomosis performed. The patient made an excellent recovery and was discharged well eighteen days later.

The microscopic section showed a tumor composed largely of a tremendous overgrowth of blood vessels. These had formed polypoid masses which had broken through the mucous membrane and projected into the lumen. The vessels varied in size from the smallest capillaries to arterioles, and were filled with fibrin. The lining endothelium was composed of a single layer of cells in some places, of several layers in others. These cells possessed a scanty amount of cytoplasm, were elongated and contained oval nuclei that stained lightly and were almost chromatin-free. The stroma consisted of scanty connective tissue which was densely infiltrated with round cells and leukocytes. The tumor had arisen from the submucous vascular plexus. The diagnosis was hemangioma.

CASE 11 (path. no. G 9819; fig. 30).—R. S., a white man, aged 78, was admitted to the Johns Hopkins Hospital, complaining of urinary frequency, nocturia and retention. Symptoms had developed over a period of eight months and had become progressively worse. The results of physical examination were essentially negative, except for the enlarged prostate. A suprapubic prostatectomy was performed, but the patient reacted very poorly from the operation. Lobar pneumonia developed, and he died on the eighth day after operation.

At autopsy, a dark red semispheroid nodule was found projecting into the lumen of the ileum 1 meter above the ileocecal valve. This tumor was continuous with a thrombosis of the mesenteric vein which extended back about 4 cm. from the intestine. The tumor lifted the mucosa up so that it was in approximation with the opposite side of the lumen, leaving only a narrow slit. On section, the tumor was 1.5 cm. in diameter, and dark red, and had split the muscle fibers apart, lifting the submucosa and mucosa together.

The microscopic section was that of a hematoma. It consisted of a dark red homogeneous mass of fibrin and old blood cells which had evidently started between the layers of the muscular stratum and split them out into a fan shape. The mesenteric vein contained an ordinary laminated thrombus which was not infected. The diagnosis was hematoma.

CASE 12 (path. no. G 7353).—I. C., a white man, aged 77 entered the Johns Hopkins Hospital, complaining of gross hematuria and frequency of urination over a period of ten months. During the latter part of the illness, incontinence, burning pain during the act and dribbling developed. Physical examination revealed the presence of a tumor of the bladder. Auricular fibrillation was a complicating feature. The hemoglobin was 45 per cent. There was a bilateral hydrocele. The tumor was diagnosed carcinoma, and operation was proposed. An attempt was made to build up the patient for operation, but pneumonia developed, and he died three weeks after admission.

At autopsy, the clinical diagnosis was confirmed. At routine examination of the intestinal tract, a polypoid tumor was found in the ileum 25 cm. above the valve. It was 1.5 cm. in diameter and hung loosely into the lumen at the end of a slender pedicle. It was very soft and flabby. On section, the interior was composed of a golden yellow homogeneous material.

Microscopic examination showed a typical lipoma. The cells were large clear droplets of fat that stained very faintly. Nuclei could not be seen in every cell, owing to the level at which the section was cut. The nuclei that could be seen, however, were small and dark and usually arranged at the outer border of the cell. The cytoplasm was surrounded by very delicate septums of connective tissue. The pedicle was composed of delicate strands of connective tissue and a few muscle fibers that had apparently been drawn up into the pedicle. Several small blood vessels were found in the base of the pedicle, but very few could be found in the substance of the tumor. It was located in the submucosa and had pushed the mucosa upward intact. The diagnosis was lipoma.

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# SUDDEN DECOMPRESSION OF THE CHRONICALLY DISTENDED URINARY BLADDER

A CLINICAL AND PATHOLOGIC STUDY

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MINNEAPOLIS

The idea that one must not empty the urinary bladder abruptly when it has been the seat of chronic retention of the urine as a result of prostatic obstruction has been accepted for many years. With the development of surgery of the prostate gland, this idea has assumed new significance, so that the majority of surgeons have adopted measures designed to empty the chronically distended bladder slowly in order to avert such serious or fatal consequences as are said to follow abrupt withdrawal of the urine. However, there is in the minds of many a suspicion that the sudden withdrawal of the urine is *per se* quite harmless. A careful survey of the literature reveals that the subject has never been studied exhaustively, nor has any conclusive evidence been presented to show that the abrupt withdrawal of "residual urine" is of itself a dangerous act. True, deaths have followed such a procedure; but they have also followed catheterization in the absence of urinary retention.

This study was undertaken in an effort to ascertain whether there is, in the kidneys or bladders of patients dying after the sudden removal of the residual urine secondary to prostatic obstruction, any pathologic lesion that may be regarded as typically the effect of sudden emptying *per se*, which does not occur in any other condition. To this end, a series of seventy-one patients has been studied. These patients presented themselves at the Mayo Clinic, Rochester, Minn., or at the University Hospital, Minneapolis, complaining of the symptoms of prostatic obstruction, and they died while under treatment.

## REVIEW OF THE LITERATURE

The idea that sudden emptying of the chronically distended bladder is perilous apparently had its origin far back in medical history. The Ebers papyrus describes a concoction the administration of which was

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Thesis submitted to the faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science.

intended to prevent the too rapid escape of urine from the bladder. The conception undoubtedly developed *pari passu* with the use of the catheter, the exact origin of which is lost in antiquity. It is known, however, that Celsus used curved metal catheters, some of which were found in the ruins of Pompeii.

One gets the impression from the literature of the present time that nearly every experienced surgeon heeds the advice of Guyon (1903) to "empty gradually and antiseptically the bladder."

Early students of the question attributed severe or fatal reactions to the mechanical effects of a sudden fall of pressure within the bladder itself; more recently it has been suggested that this fall of pressure is propagated to the kidneys and so disturbs their function as to cause severe reactions or even death. Still others hold the opinion that such reactions as are seen are due to infection of the urinary tract superimposed on the dilatation due to obstruction.

For convenience, the various theories as to the mechanism of reactions to catheterization are outlined:

*Theories of the Mechanism of the Reactions Following Bladder "Decompression"*

- I. Disturbances in the urethra and bladder of traumatic origin.
  - A. Direct trauma:
    1. Urethral hemorrhage from traumatized areas.
    2. Urinary reabsorption through traumatized areas.
  - B. Indirect trauma:
    1. Hemorrhage *ex vacuo*.
    2. Vascular injury through unaccustomed contraction of the bladder.
- II. Disturbances in the kidneys due to release of preexisting tension.
  - A. In the kidneys themselves:
    1. Congestion.
    2. Edema.
    3. Change in relative position of uriniferous tubules.
- III. Reflex nervous disturbances (syncope).
  - B. Secondary effects:
    1. Blood pressure fall.

The first report to come to my attention in which death was ascribed to catheterization of a patient with a prostatic condition was that of Chassaignac. In 1844, he recorded the death with chills and fever of an aged man a few days after catheterization. The autopsy protocol strongly suggests the presence of acute pyelonephritis. However, this condition was not recognized at that time, and Chassaignac did not attempt to explain the cause of death.

A few years later Finlayson reported a case in which he attributed the fatality to bleeding from the prostate as a result of trauma from catheterization. The patient, an aged man with a prostatic condition, developed gradually a distended bladder. Nine hundred cubic centi-

meters of urine was withdrawn at one sitting, the first being clear, the last bloody. Death ensued in forty-eight hours, and autopsy disclosed submucous hemorrhages in the bladder and intertubular and intratubular hemorrhages in the kidney. The description of the histology of the kidney is too meager to permit one to judge of the character of the underlying lesion. The author stated that he had "heard of" two more such cases. Tuffier reported two similar cases. Unfortunately, his autopsies were limited to the bladder alone.

Sedillot concluded on experimental grounds that the reabsorption of urine through areas abraded by the catheter caused uremia and death. He collected urine from patients suffering from prostatic obstruction and injected it intravenously into dogs; the animals died, and Sedillot found the kidneys sometimes congested and sometimes the seat of abscesses, which were also found in other organs. Since this work was done before the publications of Pasteur, the infectious nature of the process that resulted in death was not understood.

It was early decided that some factor other than simple acute retention must be present in order to make catheterization perilous. In 1883, Albarran pointed out that the abrupt relief of a very marked retention of short duration entailed no serious consequences. However, he did not state how long a retention must be present or to what degree the bladder must be distended in order to render sudden emptying of the bladder dangerous; nor, to my knowledge, has this been determined up to the present time. In a search for an explanation for these phenomena, Mercier called attention to the almost universal presence of congestion in the prostate, bladder, ureters and kidneys of patients dying of prostatic hypertrophy; this observation has been confirmed by Grellety, Picard, Tuffier, Genouville and Boeckel, Delbet and Chute.

The minds of most of the early investigators were focused on the bladder. Mindful of the congestion already described, Desormeaux emphasized the importance of postcatheter bleeding, which he likened to that occurring in the uterus following parturition. Albarran, Le Grand, Guyon (1879) and Blum and Rubritius were impressed by the importance of hemorrhage following catheterization. They alleged that the sudden emptying of a long-filled bladder led to a diminution of the intravesical tension to a point below that in the blood vessels. They believed that this led to bleeding "*ex vacuo*" in spite of the obvious fact that a vacuum cannot obtain in a collapsible viscus; theoretically, of course, a reduction in pressure could lead to bleeding without the occurrence of a vacuum.

Genouville and Boeckel and Ventici and LaRoche have recently put forward this theory anew.

Mercier believed that sudden contraction of the previously distended bladder so compressed the congested vesical veins that they could not empty as rapidly as the bladder contracted and so ruptured.

While the writers thus far were content to refer death to lesions of the lower part of the urinary tract, it became apparent early that fatality usually resulted from renal inadequacy. It has been assumed that there exists as a result of prostatic obstruction a constantly elevated pressure within the bladder, and that this pressure is transmitted by way of the ureters to the kidney pelvis. That such an elevation exists is evident from the frequent occurrence in patients with prostatic conditions, of hypertrophy of the bladder wall, of diverticula therein and of thickening with dilatation of the kidney pelvis and of the ureter. This assumption has been supported clinically by the observation that, if one inserts a catheter into the bladder of a patient with a prostatic condition with retention of the urine and connects it to a manometer the resultant pressure is higher than that which develops in a normal person (Adler, Dubois, Van Zwahlenburg, Bumpus and Foulds, Campbell and Rose). As will be pointed out in the comment, this observation does not necessarily support the conclusions stated. However, the idea that such a backpressure exists and that its sudden release is the exciting factor in the reactions following catheterization in retention of urine is the basis of most of the current explanations of these reactions.

The precise mechanism by which the pressure in the kidney pelvis is raised in retention of the urine is a moot point, most observers believing simply that the presence of increased pressure in the bladder requires a pressure rise in the pelvis and ureter to permit the forcing of urine into the bladder. However, Düttmann and Kreutzmann are of the opinion that the pressure increase in the renal pelvis is due to stenosis of the intramural ureter as a result of hypertrophy of the bladder musculature; Tandler and Zuckerkandl attributed it in many instances to compression of the ureter by the vas deferens. Obviously, if either of these latter theories is correct, the kidneys cannot be decompressed abruptly by emptying the bladder in any manner whatever.

Whatever the mechanism involved, it is rather obvious that the dilatation of the kidneys results from an anemia of the renal parenchyma secondary to the increased intrapelvic tension, as shown experimentally by Newman, Hinman and Morrison and Hinman and Hepler.

As early as 1876, d'Étiolles suggested that the sudden withdrawal of the retained bladder urine reduced the "backpressure" in the kidneys abruptly and led to renal congestion, inflammation and "apoplexy" with resultant serious or fatal impairment of the renal function. This view has lately been reemphasized by Thompson-Walker, Newman, Evans, Wildbolz, Bumpus (1926) and many others.

Regnault ascribed the issue to a similar fall in the "backpressure," but favored the idea that the edema rather than the congestion disabled the kidneys.

Wright has suggested that the "backpressure" in the kidney pelvis gradually distorts the uriniferous tubules so that, when this pressure is suddenly relieved, a derangement of the position of the tubules occurs and interferes seriously with the secretion of the urine.

Although many of the theories just stated have been current for half a century, no one has succeeded in establishing just what anatomic or functional changes must exist in order to render dangerous the abrupt removal of retained urine. Grellety, Picard and others have noted the presence of preexisting renal congestion. Mercier suggested that an unrecognized latent nephritis played an important rôle. Kidd has recently stated that danger is present only in uremic patients.

The only attempt to establish definite criteria is that of O'Connor. He believes that if the blood pressure is normal, the residual urine less than 400 cc. and the renal function adequate, immediate complete emptying of the bladder may be practiced safely.

It should be noted that the theories thus far cited are based on clinical experience and on deduction. Pathologic evidence supporting them is not available. It has not been shown that the kidneys, after the sudden relief of urinary retention, exhibit lesions not seen in the absence of intravesical manipulation.

The theory that the reaction to sudden removal of residual urine depends on a fall in the blood pressure was apparently first suggested by Pilcher in 1914, and has attracted many followers. It depends on the assumption previously mentioned that prostatic retention leads to a constant rise in the pressure within the renal pelvis. This in turn is said to cause a rise in the systemic blood pressure in order to insure the secretion of the urine, a hypothesis not entirely proved, since Shaw and Young and I (table 1) have found that the average blood pressure in a large series of patients with prostatic conditions with chronic retention of the urine does not exceed the average level of control patients of the same average age but without residual urine, while Elfving found normal or reduced blood pressure readings the rule in the overflow incontinence of chronic retention.

However, Pilcher observed a definite fall in the systolic blood pressure following cystotomy for the relief of urinary retention. While the fact that he used cocaine as an anesthetic diminishes the validity of his observation, Peacock soon found that the fall occurred also when the urine was removed by catheterization. O'Connor studied this phenomenon in a series of seventy-four patients with prostatic conditions and found that the fall was prompt, and that it might reach 85 mm. of mercury. He further observed that its extent could be limited and spread over a considerable period by emptying the bladder gradually.

Shaw and Young have reported a decrease in the blood pressure following the removal of residual urine, but have expressed the belief

that the fall is due largely to the relief of pain and to the subsidence of the excitement and apprehension attendant on hospital admission. They have reported three cases in which the systolic blood pressure fell promptly to 60 mm. of mercury on catheterization, but returned to an adequate level with therapeutic measures. They believed that the condition of these three patients was analogous to that of surgical shock.

Von Monakow and Mayer had previously postulated a rise in blood pressure secondary to urinary obstruction and had attributed it to a toxic vasoconstriction due to nitrogen retention or to some reflex mechanism. They regarded the fall subsequent to catheterization as a consequence of the relief of nitrogen retention in many instances. Full believed that a reflex mechanism, excited perhaps by pain, was the more important, and found that hypotension did not follow the relief of vesical distention in the presence of transverse myelitis. Grauhan thought that the decrease in blood pressure was attributable to splanchnic dilatation like that sometimes seen after the removal of ascitic fluid, a decrease that was reproduced experimentally by Wangenstein and Scott in the dog. However, as they pointed out, this phenomenon does not occur in instances of long-standing distention of the abdomen, since here the intra-abdominal structures have so accommodated themselves that the intra-abdominal pressure remains normal. Yet it is in cases of long-standing bladder distention that the effects of catheterization are said to be most serious.

Salomon believed that any hypertension persisting after catheterization was due to arteriosclerotic or atrophic kidneys. Oppenheimer attributed the rise in blood pressure that is said to occur with urinary retention to a reflex in acute cases, but he believed that retention of metabolites in chronic cases led to a toxic vasoconstriction with hypertension. Elfving, however, found in many instances a fall in blood pressure with nitrogen retention in prostatism. Both Oppenheimer and Elfving attributed the fall in blood pressure following catheterization to the development of acute pyelonephritis, while the latter emphasized the fact that any minor operative procedure, such as vasectomy, or any febrile disorder may lead to the development of hypotension in the presence of urinary retention.

The theories thus far discussed depend only on mechanical factors. Soon after the discoveries of Pasteur, however, the idea was advanced that infection might be responsible for catheter reactions.

It is known, both on clinical and on experimental grounds, that the presence of urinary retention is one of the most potent factors predisposing to infection of the urinary tract. Albarran and Hallé, Achard and Regnault, Schmidt and Aschoff, Bazy, Rovsing, and Melchior have found that the injection of virulent bacteria into the intact animal bladder does not suffice to produce more than a transitory cystitis unless the bladder

is traumatized or obstructed, whereupon severe infection, not alone of the bladder but also of the upper part of the urinary tract, often develops. Cabot has emphasized the importance of distention of the bladder in postoperative urinary retention as predisposing to infection of the urinary tract. When a patient with a prostatic condition with urinary retention is catheterized, there are almost invariably present all of these requisites for the production of infection. Cauvet and Escat early described congestion, edema and purulent infiltration in the kidneys of patients dying after catheterization, and they ascribed these changes to acute ascending infection.

Escat, Chute and Hyman have called attention to the fact that pyelonephritis may lead to gross bleeding from the kidney.

That bleeding after sudden emptying actually does originate at times in the kidneys themselves has been demonstrated conclusively by Shaw and Young, who performed cystoscopy on several patients with prostatic conditions during the bleeding that followed catheterization and observed bloody urine issuing from the ureteral meatus. They did not, unfortunately, report cultural studies of the urine in these instances.

Nervous shock or syncope was called on to explain an occasional sudden death by Guyon (1879), Cauvet and many others. Shaw and Young have recently suggested that some such factor may be involved occasionally. The patients they observed, however, survived, while those of the older writers did not receive complete autopsy studies. The possibility that such deaths may be due to demonstrable extrarenal organic lesions will be taken up in the comment. It seems to me that syncope and shock are convenient terms to be reserved for those occasions on which fatality is inexplicable even after a thorough postmortem examination.

Works in pathology describe the renal changes of prostatic obstruction at some length, but are silent on the topic of sudden emptying of the bladder and its effect on the kidneys. It must be remembered that the brief references already made to pathologic changes in the kidneys secondary to sudden emptying of the bladder are theoretical and not based on changes actually demonstrated.

While Kaufmann and Young have stated that the changes in the kidney secondary to prostatic obstruction are similar to, if not identical with, those following ureteral obstruction, the pure obstructive element is so often complicated and masked by arteriosclerotic and infectious lesions that comparisons are difficult or unsatisfactory. Whether there is any difference in the anatomic nature of the lesions produced by pure obstruction at the bladder neck as compared to those resulting from obstruction of the ureters has not been determined. Only the latter have been studied experimentally. Enderlen in 1904 ligated a dog's ureter and found that dilatation of the pelvis and ureter as well

as of the renal tubules themselves soon developed. He described small areas of parenchymal necrosis that led later to interstitial fibrosis. Rautenberg performed similar experiments on the rabbit and had similar results in all respects. Orth emphasized the fact that there was surprisingly little glomerular injury even in advanced hydronephrosis, an observation confirmed by many other investigators.

Johnson found only a simple atrophy of the kidney substance with but slight tubular dilatation to result from ureteral occlusion, and Bell is inclined to attribute the development of marked tubular dilatation, lymphocytic infiltration and fibrosis to complicating factors such as infection and arteriosclerosis.

Wade has observed the same lesions of hydronephrosis in patients dying of renal insufficiency secondary to prostatic hypertrophy.

A variety of procedures has been advocated to combat the danger of sudden relief of chronic vesical distention. Probably the earliest method, and certainly that which has enjoyed the most enduring favor, is that suggested by Mercier in 1844. He suggested either fractional emptying of the bladder by repeated catheterization, or prompt withdrawal of all of the residual urine, followed at once by partial replacement with an antiseptic solution.

Genouville and Boeckel and Michon have favored the abrupt relief of retention by cystostomy, believing that the bladder having been opened, the intravesical tension will be replaced by the atmospheric pressure, and harm will be averted. An additional benefit of this method is said to be an avoidance of trauma of the congested wall of the urethra and bladder.

Von Zwahlenburg in 1920 introduced the principle of continuous secretion against a gradually diminishing column of urine, which has since found very wide favor. Scott has recently suggested the use of a very small (no. 5 French) indwelling urethral catheter with the idea that its narrow lumen will prolong emptying for about twenty-four hours.

#### STUDY OF CASES

*Clinical Features.*—This paper is based on the clinical and autopsy observations of seventy-one patients who presented themselves at the University Hospital or at the Mayo Clinic with urinary retention due to prostatic hypertrophy, and who died while under treatment. The whole group has been divided into three main subgroups (table 2). Group I consists of those patients having more than 500 cc. or residual urine; group II consists of those having less than 500 cc. of residual urine, while group III is composed of two patients who died with bladders distended as a result of prostatic obstruction without having been catheterized. Groups I and II have been further subdivided into



TABLE 1.—Data in Cases Examined

No.	Age	Years	Dura- tion, Urine, phos- phate, Cc.	Phenol- sul- phate, Cc.	Urea	Blood Pres- sure	Pus	Hema- turia	Oil- guria	Time of Survival, Days	Lesions of the Kidney GROUP I	Lesions of the Bladder	Cause of Death	Emptying
1	64	2	All	..	75	170/100	1	0	0	14	Dilatation I of pelvis and ureter; interstitial round cell infiltration and fibrosis I; acute diffuse pyelonephritis IV; arteriosclerosis II; interstitial congestion and hemorrhage IV	.....	Renal insufficiency	Abrupt
2	86	1	All	..	..	210/130	..	..	..	12	Chronic pyelonephritis III; arteriosclerosis II; acute pyelonephritis with multiple abscesses	Chronic cystitis with acute congestion; bladder filled with purulent urine	Renal insufficiency	Abrupt
3	75	5	All	..	..	180/80	3	..	*	9	Chronic pyelonephritis I; acute diffuse pyelonephritis III; dilatation I of pelvis, ureter	Small carcinoma of fundus	Renal insufficiency	Abrupt
4	64	5	900	..	..	120/?	1	..	..	12	Dilatation I of pelvis, ureter; chronic pyelonephritis III; arteriosclerosis II; acute pyelonephritis with multiple abscesses	.....	Renal insufficiency	Abrupt
5	70	2	All	25	..	.....	2	+	..	12	Dilatation III of pelvis, ureter; chronic pyelonephritis III; acute pyelonephritis with multiple abscesses IV	Bladder distended by blood-tinged, purulent urine; acute suppurative prostatitis	Renal insufficiency	Abrupt
6	64	1	1,000	5	..	145/90	3	+	..	25	Dilatation II of pelvis, ureter; chronic pyelonephritis III; acute pyelonephritis with multiple abscesses; small right perinephric abscess	Congestion of wall; areas of granulation tissue; chronic cystitis	Renal insufficiency	Abrupt
7	73	15	All	..	..	125/85	2	+	+	19	Dilatation IV of pelvis, ureter; chronic pyelonephritis III; diffuse acute pyelonephritis with necrosis and multiple abscesses; interstitial congestion and hemorrhage III	.....	Renal insufficiency	Abrupt
8	59	4	600	0	..	130/80	2	+	..	33	Dilatation of pelvis, ureter; chronic pyelonephritis III with pyonephrosis; acute pyelonephritis with multiple abscesses II	Blood-tinged, purulent urine; areas of ulceration; chronic cystitis	Renal insufficiency	Abrupt
9	86	7	2,500	..	..	.....	2	+	..	10	Dilatation of pelvis, ureter III; chronic pyelonephritis III; acute diffuse pyelonephritis II; congestion and hemorrhage IV	Slightly bloody urine; purulent cystitis	Renal insufficiency	Abrupt
10	67	2	850	15	..	170/100	3	0	..	11	Dilatation II of pelvis, ureter; chronic pyelonephritis III; congestion II; arteriosclerosis I	.....	Renal insufficiency	Abrupt
11	87	1½	1,000	10	..	.....	3	..	0	2	Dilatation III of pelvis, ureter; chronic pyelonephritis III	Purulent urine; chronic cystitis; congestion	Renal insufficiency	Gradual
12	62	15	All	..	200	100/55	3	0	0	20	Dilatation II of pelvis, ureter; unilateral fused kidney; chronic pyelonephritis III	Hemorrhagic cystitis	Renal insufficiency	Gradual

[illegible]

TABLE 1.—Data in Cases Examined—Continued

No.	Age	Years	Resid- ual sul- tion, Urine, phos- phate	Urea	Blood Pres- sure	Pus	Hema- turia	Off- viva	Time of Survival, Days	Lesions of the Kidney	Lesions of the Bladder	Cause of Death	Emptying Gradual	
29	56	2	All	0	155	160/80	2	0	0	30	Dilatation II of pelvis, ureter; chronic and acute pyelonephritis with abscesses III; congestion II	Purulent cystitis .....	Renal insufficiency; pyemia	Gradual
30	65	3	All	0	425	120/80	2	0	0	8	Dilatation IV of pelvis, ureter; chronic pyelonephritis IV with pyonephrosis; congestion I; arteriosclerosis II	Diverticulum; purulent diverticulitis; congestion of mucosa; hemorrhages in submucosa	Renal insufficiency	Gradual
31	68	3	All	..	320	130/95	4	+	0	11	Dilatation I of pelvis, ureter; chronic and acute pyelonephritis with abscesses III; arteriosclerosis IV	Chronic cystitis with congestion	Renal insufficiency	Gradual
32	61	1	All	..	70	150/100	2	0	0	19	Dilatation III of ureter, pelvis; chronic pyelonephritis III; arteriosclerosis IV; congestion II	Gangrenous cystitis with ulceration and congestion; purulent urine	Pulmonary embolism	Gradual
33	57	1	All	..	380	180/90	3	+	0	8	Dilatation III of pelvis, ureter; chronic pyelonephritis and acute with multiple abscesses IV; congestion III; arteriosclerosis III	Chronic cystitis with congestion	Renal insufficiency	Gradual
34	70	1	All	..	280	165/80	3	0	0	8	Dilatation III; chronic and acute pyelonephritis with abscesses; congestion II; arteriosclerosis III	Diverticulum; blood-tinged urine; submucous hemorrhages	Renal insufficiency	Gradual
35	69	4	All	..	300	130/100	3	0	..	18	Dilatation III; chronic and acute pyelonephritis with abscesses III	Diverticulum; stone; chronic cystitis with marked congestion	Renal insufficiency	Gradual
36	59	2	All	..	60	160/140	4	0	0	11	Dilatation II; chronic and acute pyelonephritis with abscesses III	Gangrenous cystitis ...	Renal insufficiency	Gradual
37	66	3	All	..	280	140/90	1	0	0	9	Dilatation III; chronic and acute pyelonephritis III with abscesses	Bloody urine; congestion of and exudate on mucosa	Renal insufficiency	Gradual
38	67	1	All	..	330	160/90	2	0	0	9	Dilatation III; chronic and acute pyelonephritis with abscesses IV; congestion II; arteriosclerosis II	Chronic cystitis with congestion	Renal insufficiency	Gradual
39	62	6	600	0	330	160/80	2	0	0	9	Dilatation III; chronic pyelonephritis IV, with atrophy; congestion IV	Stone; hemorrhages of submucosa	Renal insufficiency; cardiac infarct	Gradual
40	83	10	All	10	175	135/75	1	+	0	63	Chronic and acute pyelonephritis with abscesses IV; congestion IV; arteriosclerosis I	No data .....	Renal insufficiency	Gradual
41	72	8	1,000	..	310	150/110	4	+	+	10	Dilatation IV; chronic pyelonephritis III	No data .....	Renal insufficiency	Gradual

42	73	3	800	..	290	160/100	0	..	21	Dilatation II; chronic pyelonephritis III; acute pyelonephritis with abscesses	No data	Renal insufficiency	Gradual	
43	63	6 mo.	600	..	125	145/ 85	4	..	13	Chronic and acute pyelonephritis with abscesses; ureteral without pelvic dilatation	No data	Renal insufficiency	Gradual	
44	63	10	850	..	105	.....	4	..	21	Dilatation IV; chronic pyelonephritis IV with acute pyelonephritis with abscesses IV	No data	Renal insufficiency	Gradual	
45	67	6 mo.	All	..	315	160/ 80	1	+	9	Dilatation II; chronic pyelonephritis III with acute pyelonephritis and abscesses III	No data	Renal insufficiency	Gradual	
46	79	10	All	..	25	170/ 60	1	..	9	Dilatation II; chronic pyelonephritis II with acute pyelonephritis and abscesses IV	No data	Renal insufficiency	Gradual	
47	73	1	All	..	120	.....	0	..	35	Chronic pyelonephritis III; acute III with abscesses	No data	Renal insufficiency	Gradual	
GROUP II														
1	72	5	240	35	40	160/ 90	2	0	..	8	Advanced interstitial round cell infiltration and fibrosis I; tubular dilatation; arteriosclerosis I; dilatation I of pelvis, ureter	.....	Renal insufficiency; bronchopneumonia	Abrupt
2	77	10	200	..	..	.....	2	..	15	Dilatation II of pelvis, ureter; chronic pyelonephritis II; acute pyelonephritis IV with multiple abscesses	Chronic cystitis with purulent urine	Renal insufficiency	Abrupt	
3	61	3	500	..	..	.....	0	+	7	Dilatation of pelvis, ureter; chronic pyelonephrosis IV; interstitial congestion and hemorrhage III	Distended with bloody urine; chronic cystitis with congestion	Renal insufficiency; acute bacterial endocarditis	Abrupt	
4	60	6	300	..	..	200/140	0	+	12	Dilatation III of pelvis, ureter; chronic pyelonephritis IV; acute diffuse pyelonephritis II; interstitial congestion I	Congestion of mucosa; blood-tinged urine	Renal insufficiency	Abrupt	
5	80	1	60	..	..	175/110	2	+	23	Dilatation I of pelvis, ureter; chronic pyelonephritis II	Slightly blood-tinged urine	Lobar pneumonia	Abrupt	
6	56	1	100	30	..	120/ 80	0	+	49	Chronic pyelonephritis III; arteriosclerosis II; congestion II	Chronic cystitis	Renal insufficiency	Abrupt	
7	63	3	100	..	..	180/120	3	+	22	Dilatation of pelvis, ureter II; chronic pyelonephritis II; interstitial congestion and hemorrhage III; arteriosclerosis III	Purulent membranous cystitis	Renal insufficiency	Abrupt	
8	72	6	250	..	..	150/ 90	0	+	2	Dilatation II of pelvis, ureter; chronic pyelonephritis II; arteriosclerosis II	Diverticulum; edema of perivesical tissue; chronic cystitis with congestion; purulent blood-tinged urine	Renal insufficiency	Abrupt	
9	71	8	250	20	40	150/100	2	+	18	No dilatation; chronic pyelonephritis III; arteriosclerosis II; acute pyelonephritis IV with multiple abscesses	.....	Pulmonary embolism	Gradual	
10	65	7	100	25	..	180/100	3	+	12	Dilatation I of pelvis, ureter; chronic pyelonephritis III with acute, multiple abscesses IV; interstitial congestion and hemorrhage IV	Chronic catarrhal cystitis	Renal insufficiency	Abrupt	

TABLE 1.—Data in Cases Examined—Continued

No.	Age	Years	Resid.-Phenol- sul- tion, Urine, phos- phate	Urea	Blood- Pres- sure	Pus	Hema- turia	Oli- viva, Days	Time of Sur- vival, Days	Lesions of the Kidney	Lesions of the Bladder	Cause of Death	Emptying
11	62	8	0	25	..	120/80	0	0	..	24	Chronic pyelonephritis II; congestion III; many hyaline glomeruli	Suppurative seminal vesiculitis	Abrupt
12	64	1/2	100	..	..	130/100	2	0	..	9	Dilatation IV of pelvis, ureter; chronic pyelonephritis III; acute with multiple abscesses IV	Renal insufficiency	Abrupt
13	72	5	300	35	40	125/80	4	0	..	10	Dilatation II of pelvis, ureter; chronic pyelonephritis III; acute with multiple congestion III; subcapsular hemorrhage	Renal insufficiency	Abrupt
14	64	1 mo.	500	5	..	160/80	2	0	+	6	Chronic pyelonephritis III.....	Hemopurulent cystitis..	Abrupt
15	67	..	500	5	..	.....	3	+	0	16	Chronic pyelonephritis II; diffuse acute pyelonephritis with multiple abscesses IV; arteriosclerosis I	Multiple diverticula ....	Abrupt
16	67	12	150	60	..	170/100	0	0	0	60	Chronic pyelonephritis I; congestion and hemorrhage I; acute pyelonephritis with necrosis II	Phlegmonous cystitis; prostatic abscess	Abrupt
17	63	4	15	50	40	150/80	1	0	0	12	Chronic pyelonephritis I; congestion I....	.....	Abrupt
18	66	3	400	50	..	180/120	0	0	++	35	Chronic pyelonephritis II; arteriosclerosis I	Hemocatarrhal cystitis	Abrupt
19	70	3	150	0	365	150/85	4	0	0	5	Acute and chronic pyelonephritis IV with multiple abscesses and necrosis	Purulent cystitis .....	Abrupt
20	56	10	120	50	50	120/80	1	0	0	30	Acute pyelonephritis with multiple abscesses IV; congestion and interstitial hemorrhage IV	Slight congestion; diverticulum	Gradual
21	59	4	500	..	50	160/110	3	+	0	14	Dilatation III; chronic and acute pyelonephritis with abscesses IV; congestion III; arteriosclerosis I	Diverticulum; purulent cystitis	Gradual
22	63	4	400	..	180	120/75	0	+	0	10	Dilatation IV; chronic and acute pyelonephritis with abscesses IV	.....	Gradual
1	49	2	...	25	..	120/70	0	0	0	†	GROUP III Chronic pyelonephritis I; congestion II; arteriosclerosis II	Renal insufficiency	Gradual
2	85	..	500	..	..	.....	0	0	+	†	Dilatation IV of pelvis, ureter; chronic pyelonephritis III	Hemosuppurative cystitis	0
											.....	Acute bacterial endocarditis	0
											.....	Renal insufficiency (never catheterized)	0

\* The twenty-four hour output of urine was less than 1,000 cc.  
† This occurred on the last day.  
‡ Not catheterized, control.  
§ The lesions were graded I to IV, according to the severity.

TABLE 2.—*Comparison of Clinical Data* \*

Group Ia		Group Ib		Group IIa		Group IIb		Group III		Control		All Fatal	
No.		No.		No.		No.		No.		No.†		No.	
34	67.5 yr.	13	68.0 yr.	5	64.8 yr.	17	66.7 yr.	2	67 yr.	100	64.6 yr.	71	65.4 yr.
34	3.7 yr.	13	3.6 yr.	5	5.8 yr.	17	4.6 yr.	2	.....	100	5.1 yr.	71	3.8 yr.
34	91.6%	13	100.0%	5	80.0%	17	53.8%	2	0	100	85%	68	91.6%
20	200 mg.	3	60 mg.	5	140 mg.	3	40 mg.	2	.....	100	30 mg.	45	185 mg.
12	10%	6	18%	3	28%	10	30%	1	25%	100	35%	32	20%
34	155/85	13	150/90	5	140/90	17	145/90	1	120/90	100	150/85.	62	145/87
29	48.3%	10	70%	5	60%	16	50%	0	.....	...	.....	61	52.4%
29	17.2%	5	60%	5	0%	8	37.5%	0	.....	...	.....	48	22.9%
34	10.4 da.	13	15.0 da.	5	15.4 da.	17	18.3 da.	0	.....	...	.....	69	15.6 da.
34	500 cc.	13	500 cc.	5	0-500 cc.	17	0-500 cc.	2	Distended	100	250 cc.	69	500 cc.

\* Group Ia consists of patients with 500 cc. or more of residual urine whose bladders were drained gradually; group Ib, those with 500 cc. or more of residual urine whose bladders were drained abruptly; group IIa, those with 500 cc. or less of residual urine whose bladders were drained gradually; group IIb, those with 500 cc. or less of residual urine whose bladders were drained abruptly; group III, those with distended bladders who were not catheterized.

† Number of cases in which data were available.

those whose bladders were "decompressed" gradually in from one to five days (a), and those whose bladders were emptied promptly at a single session (b).

This subdivision has been employed in order to ascertain whether the character of the lesions found at autopsy could be correlated with the degree of distention of the bladder, with the manner in which the bladder was emptied, or, indeed, whether the act of emptying the bladder itself influenced the type of lesion in the urinary tract.

In order to ascertain whether the patients in the various groups had lesions of comparable severity before catheterization, clinical data concerning them have been studied (table 2), and, in addition, the same data have been obtained from a group of one hundred consecutive patients who survived prostatectomy in order to ascertain, if possible, what factors led to the fatal issue.

Unfortunately in many of the earlier cases, studies of the kidney function were not made, and since it is in the kidney function alone that significant differences in the various groups are evident, this fact robs the following data of much of their value.

The average age in each group is essentially the same, and it is interesting that the duration of symptoms averaged 1.3 years longer in the survivors than in those who succumbed. However, it has been my experience that the man in the prostatic age is rather complacent about his minor difficulties, so that his statements as to the duration of his difficulties are open to doubt. The information concerning the presence or absence of infection, too, is not wholly reliable. In many instances, only a single urine was examined before catheterization. Since it is common knowledge that even in severe cystitis the voided urine may be relatively free from pus at times, conclusions based on the examination of a single specimen must be guarded. However, pyuria was found before treatment in 85 per cent of the survivors and in 91.6 per cent of those who died.

It is in the kidney function as demonstrated by the urea of the blood that the first striking difference is noted. That of the survivors is well within normal limits (30 mg.), while that in the fatal cases averaged 185 mg. for each 100 cc. of blood on admission. Only in group II b (those catheterized at one sitting of less than 500 cc. of residual urine) was the blood urea normal, and here, unfortunately, it was estimated in but three of seventeen patients. Neither of the cases in group III were investigated.

The differences in phenolsulphonphthalein excretion correspond to those in the blood urea, but are somewhat less striking. The average phenolsulphonphthalein excretion of those who subsequently underwent successful prostatectomy was 35 per cent in one hour, while those who died eliminated but 20 per cent in the same period. Unfortunately,

however, the dye excretion was investigated in less than one half (thirty-two of seventy-one) of the fatal cases.

There were no striking differences in the blood pressures in the various groups, all coming well within the limits to be expected in the ages involved.

The occurrence of hematuria as evidence of some specific response to sudden emptying of the bladder has been emphasized by many writers. It was noted in 50.8 per cent of the fifty-nine fatal cases in which records were available, but was never mentioned as a factor in the fatal outcome. It occurred in 53.8 per cent of twenty-six cases in which emptying was carried out abruptly as compared to 48.5 per cent of thirty-three cases in which emptying was carried out gradually, in which records were complete; it was not definitely more frequent in patients with more than 500 cc. of residual urine (50.2 per cent of those with 500 cc. or more, and 47.6 per cent of those with less than 500 cc. of residual urine).

The question of the degree of diminution in the urinary output following sudden emptying of the bladder remains unsettled. In this group, although forty patients were catheterized abruptly, records of the urinary output were kept in but thirteen. Of these, five had a residual urine of more than 500 cc. and eight of less than 500 cc. Diminution of the output was noted in 60 per cent of the first and in 37.5 per cent of the second group, an average of 61 per cent as compared to 14.7 per cent with slow emptying. However, when one considers that the lowest observed twenty-four hour output was 500 cc. and that most of the patients were being sweated by means of hot packs, one cannot draw worthwhile conclusions from these data, more particularly since the groups are so small.

The manner in which the bladder was emptied evidently had very little influence on the length of survival after catheterization. Of the thirty-nine in which gradual emptying was practiced, the average survival was 11.05 days, while those who were simply catheterized lived on the average 17.2 days. The patients with 500 cc. or more of residual urine survived for a shorter period than did those with 500 cc. or less (11.9 and 17.6 days, respectively).

#### PATHOLOGIC FINDINGS

This discussion will be confined to the lesions observed in the kidneys and the bladder, since the changes in the prostate incident to prostatic hypertrophy have been discussed so fully in the literature, and since the ureters were not usually preserved for examination. The same grouping of the cases has been employed as in the discussion of the clinical findings.

The gross feature that first attracts attention in these cases is ureteropelvic dilatation. Of the sixty-nine cases in which records were



available, dilatation was present in fifty-three, or 76.8 per cent. The relationship of this dilatation to the amount of residual urine is emphasized by the fact that some measure of hydronephrosis was evident in 85.1 per cent of those in group I (500 cc. or more of residual), as compared to 63.6 per cent of those in group II (less than 500 cc. of residual).

Many other gross changes were noted, but were not described in sufficient detail to permit of their classification. Thinning of the parenchyma was, in general, proportional to the degree of pelvic dilatation. The weight of the kidneys was usually increased. Cloudy swelling was noted in the patients dying of acute infection. The presence of exudate on the pelvic mucosa was common. It is impossible from the available descriptions to attempt to separate the cases of "ascending" infection from those of "hematogenous" origin. Medullary streaks were common. When abscesses occurred, they showed no predilection for the cortex or the medulla, the two layers being about equally involved.

TABLE 3.—*Lesions of the Kidney Found at Autopsy*

	Fatal Cases		Group Ia		Group Ib		Group IIa		Group IIb		Group III	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
Chronic pyelonephritis.....	70	98.5	31	91.1	13	100.0	5	100.0	17	100.0	2	100.0
Pyonephrosis.....	3	4.2	2	5.8	1	7.6	0	0.0	0	0.0	0	0.0
Acute and chronic pyelonephritis	52	73.3	20	58.8	1	7.6	5	100.0	6	35.2	0	0.0
Normal kidney.....	1	1.4	1	2.9	0	0.0	0	0.0	0	0.0	0	0.0
Arteriosclerosis.....	27	38.0	17	50.0	4	30.7	2	40.0	2	11.7	1	50.0
Congestion, hemorrhage.....	36	50.7	14	41.1	1	7.6	2	40.0	8	47.0	1	50.0
Dilatation of pelvis and ureter...	53	76.8	28	82.3	12	92.3	2	40.0	12	70.5	1	50.0

In one instance, hemorrhage into the perinephric fat was noted (group II, case 13) and in another, suppurative perinephritis (group I, case 6).

Sections were available for microscopic study in all cases (table 3). Whenever the original section was not such as to permit the drawing of conclusions, new blocks were secured and sections made. One normal section was seen, and was taken from a patient who died abruptly following the intravenous administration of mercurochrome-220 soluble (case 48). In every other instance lesions were noted. It is impossible to say exactly where the changes of uncomplicated obstruction end and those of chronic infection begin. As has been pointed out, in many instances round cell infiltration and fibrosis of the interstitial tissue together with degenerative changes in the tubules have been observed clinically and produced experimentally by simple ureteral obstruction. However, no effort was made to exclude the possibility of infection in such cases by cultural study. I am inclined to follow Bell and to attribute these lesions (round cell infiltration, fibrosis; tubular degeneration), especially in view of their severity in this series of cases, to

infection (chronic pyelonephritis). These changes were seen in every instance except the one already noted, and were sufficiently striking to attract attention even on superficial inspection. The tendency for this process to spare the glomeruli, which has been interpreted by various investigators as evidence of typical obstructive change, was not noted in this group of cases. In all instances in which tubular or interstitial changes were advanced, the integrity of the glomeruli was correspondingly impaired. If it is true that glomerular survival bespeaks obstruction rather than infection, these observations support my inclination to regard the lesions here described as infectious.

Of the whole group, 98.5 per cent exhibited chronic pyelonephritis as described. In 30.9 per cent, it was the only lesion to be found in the kidneys.

Seventy-three and three-tenths per cent of the whole group (table 3) presented the changes of acute pyelonephritis, varying in degree from the presence of a few polymorphonuclear leukocytes in the tubules and interstitial tissue to a diffuse purulent infiltration of the whole organ. Secondary changes varied from slight granular degeneration of the tubules to widespread necrosis of tubular and glomerular epithelium. Involvement of the glomeruli seemed to be determined by contiguity to the process in the tubules. Arteriosclerosis was noted in 38 per cent, and interstitial congestion and hemorrhage in 50.7 per cent.

Of those in whom decompression was done gradually, the changes of acute pyelonephritis were present in 58.8 per cent of those with more than 500 cc. of residual urine and in all of those with less than that amount, an average of 64.1 per cent. In those in whom emptying was done suddenly, these lesions were found in 7.6 per cent of group I and in 35.2 per cent of group II, an average of 23.3 per cent.

Only two conclusions can be drawn from these figures: (1) The patient with prostatic obstruction who dies after catheterization presents infective lesions in dilated kidneys; (2) the incidence of acute lesions is nearly three times as great in those in which emptying is done gradually as compared to those in which emptying is done abruptly. Since, as has been stated previously, obstruction or trauma, or both, is essential to the experimental production of infection of the urinary tract (except by intravenous injection of bacteria) and since these conditions are present and prolonged in gradual decompression, the latter fact is not surprising.

An attempt has been made to classify the lesions of the bladder, but has been unsatisfactory (table 4). Descriptions were available in but fifty-one of seventy-one cases, and the specimens had been discarded in all but a few cases. The descriptions were rather vague, and the terminology used was variable. From table 4 it will be seen that of the fifty-one cases in which data are available the lesion was frankly infec-

tious in forty-eight, or 94 per cent. Of the remainder, submucous hemorrhages were noted in two (both patients were relieved gradually of more than 500 cc. of residual urine; a small carcinoma of the bladder fundus was found in the third).

One can conclude from these scanty data, relating to vesical lesions, only that catheterization of the patient with a prostatic condition often leads to infection of the bladder.

*The Cause of Death.*—In order to ascertain whether the method of catheterization has any influence on the cause of death, the cases have been analyzed from this aspect. It was difficult to determine in many

TABLE 4.—*Lesions of the Bladder*

Lesion	Group Ia	Group Ib	Group IIa	Group IIb	Group III
Purulent cystitis.....	7	5	1	5	1
Gangrenous cystitis.....	7	0	0	0	0
Chronic cystitis.....	1	2	0	3	0
Chronic cystitis with congestion.....	9	1	1	4	0
Hemorrhagic cystitis.....	1	0	0	0	0
Submucous hemorrhages.....	2	0	0	0	0
Carcinoma of fundus.....	0	1	0	0	0

TABLE 5.—*The Causes of Death*

Cause	Fatal Cases (71 Cases)		Group Ia (34 Cases)		Group Ib (13 Cases)		Group IIa (5 Cases)		Group IIb (17 Cases)		Group III (2 Cases)	
	Per		Per		Per		Per		Per		Per	
	No.	Cent	No.	Cent	No.	Cent	No.	Cent	No.	Cent	No.	Cent
Uremia due to.....	56	78.8	27	79.4	13	100.0	3	60	12	70.6	1	50
Chronic pyelonephritis.....	16	28.6	7	26.0	3	23.1	..	..	5	41.7	1	100
Chronic and acute pyelonephritis.	40	71.4	20	74.0	10	76.9	3	100	7	58.3	..	..
Extrarenal complications.....	15	21.7	7	21.6	..	....	2	40	5	29.4	1	50
Pulmonary embolism.....	4	26.6	2	28.5	..	....	1	50	..	....	1	50
Bacterial endocarditis.....	2	13.3	1	14.2	..	....	..	..	1	20.0	..	..
Coronary thrombosis.....	1	6.6	1	14.2	..	....	..	..	..	....	..	..
Pyemia.....	2	13.3	1	14.2	..	....	1	50	..	....	..	..
Suppurative seminal vesiculitis....	2	13.3	..	....	..	....	..	..	2	40.0	..	..
Peritonitis.....	1	6.6	1	14.2	..	....	..	..	..	....	..	..
Lobar pneumonia.....	1	6.6	..	....	..	....	..	..	1	20.0	..	..
Bronchopneumonia.....	1	6.6	..	....	..	....	..	..	1	20.0	..	..
Mercurochrome.....	1	6.6	1	14.2	..	....	..	..	..	....	..	..

instances precisely what caused the lethal outcome, and the classification that has been adopted has many disadvantages. Those cases in which the pathologic diagnosis included "uremia" may arise from such a variety of causes; uremia may mean so little or so much in the ultimate outcome. However, in each instance the pathologic lesions found at autopsy have been enumerated in order to make evident the combination of circumstances that led to death.

In the whole group a clinical diagnosis of uremia was made in 78.8 per cent, while obvious extrarenal complications were fatal in 21.2 per cent (table 5).

From a consideration of table 5 it is evident that the uremia was due in 71.4 per cent to chronic and in 28.6 per cent to acute pyelo-

nephritis; thus death probably resulted from an infectious process in the kidney of which the uremia was merely a secondary manifestation.

In four of the six deaths not directly attributed to an infectious process, pulmonary embolism was found. This process, of course, usually originates in an infected thrombosis of a systemic vein.

To summarize: The patient with a prostatic obstruction who dies after catheterization dies of an infectious process. If this process is localized in the kidneys, the clinical syndrome of uremia is often produced and may dominate the picture, although death is usually due to toxemia from infection. In about 20 per cent of the cases, the dominant lesion is extrarenal, and occasionally it may be unrelated to the catheterization (coronary thrombosis).

#### COMMENT

Every mechanism herein discussed by which sudden emptying of the bladder may lead to death is based on theoretical concepts. The cornerstone of nearly all of the theories is the accepted belief that a heightened intravesical pressure exists in prostatic hypertrophy, and that this pressure is transmitted to the kidneys. It is the relief of this pressure that is alleged to be perilous.

The exact mechanism by which this pressure is transmitted to the kidneys is not clear. Sampson and many subsequent workers, particularly Gruber, have shown that in man the oblique course of the intramural ureter and the presence of the ureterovesical valves effectively prevent reflux of bladder urine up the ureters. Pilcher, Quinby and Blum and Rubritius have found that the ureteral meatus is usually normal in appearance in the patient with prostatic enlargement, while Bumpus (1924) and Caulk have noted reflux of contrast medium up the ureters in but 4.5 and 6 per cent, respectively, of patients with prostatic conditions. Thus, direct backward transmission of the vesical pressure, through an uninterrupted column of urine, does not usually occur.

If it is merely a question of a necessary rise in intrapelvic tension to force urine past the intramural ureter that has been compressed by the increased bladder pressure, then one can conceive of a sudden release of this pressure by the urethral catheter; if this is so, one must bear in mind how variable is the quantity of residual urine and must therefore consider the possibility of spontaneous "decompression." If, on the other hand, the view of Düttmann and Kreutzmann that the pressure is due to stenosis of the intramural ureter from hypertrophy of the vesical musculature or that of Tandler and Zuckerkandl that the vas deferens compresses the ureter is correct, it is impossible to see how sudden emptying of the bladder can "decompress" the kidneys, since the force causing the backpressure would be operative as well after as before catheterization.

Moreover, death has been seen in this series of cases to follow catheterization when residual urine was not present (group II, cases 11, 17, and 19); decompression cannot be said to have occurred. Yet lesions were produced which were identical with those in patients who did have residual urine in large amounts. Further still, in 23.2 per cent of the cases, evidence of "backpressure" has been lacking at autopsy; i. e., there was no evidence of ureteral or pelvic dilatation.

There is a tendency among some observers to place a great deal of emphasis on the occurrence of hematuria following the removal of residual urine and to think that it is especially significant as part of the typical untoward reaction to sudden catheterization *per se*. This seems to me to be unwarranted for a number of reasons.

Gross hematuria occurs independently of instrumentation in a fairly respectable proportion of patients with prostatic conditions, as has been pointed out previously by Bernard, Albarran, Ventici and LaRoche, Sedillot, Escat, Kenneth Walker and Young.

It was believed by many of the earlier writers that hematuria resulted from trauma from the catheter (Finlayson and Tuffier), and Escat stated that he had never observed hematuria when the catheter passed with ease.

Young found that 3.6 per cent of his series of nine hundred eighty-three patients with prostatic conditions had had spontaneous hematuria in the absence of stone; of those with large amounts of residual, 14.1 per cent had spontaneous hematuria.

Hematuria occurs even with the methods designed to insure gradual emptying of the bladder. Van Zwalenburg's patient bled, and Bumpus and Foulds observed hematuria in 13.2 per cent of eighty-three cases in which decompression was done gradually by Van Zwalenburg's method. In the series already reported in this paper, hematuria was noted in 48.5 per cent of thirty-three fatal cases in which emptying was done slowly.

Albarran was able to produce hematuria experimentally by simple urethral occlusion in the dog. I have observed spontaneous gross hematuria in each of three dogs in which I was able to establish chronic incomplete urinary retention by partial ligation of the urethra. Each of these animals had at autopsy multiple abscesses in dilated kidneys and gangrenous inflammation in the dilated, hypertrophied bladder. No intravesical manipulations of any kind had been carried out.

Escat, Chute and Hyman have observed hematuria as a result of pyelonephritis, an observation supported by the experiments already recorded and by the autopsy observations in this series (table 6). Hematuria was known to have occurred in thirty of the patients whose records were complete. In twenty of these, or 66.6 per cent, the patient had acute pyelonephritis with multiple abscesses; six more had chronic pyelonephritis, and four had pyonephrosis as well. In no instance was

there any doubt as to the presence of an infectious process in the kidneys.

That hematuria may accompany acute pyelonephritis without urinary retention is evidenced by a patient seen by me; he was a boy of 19 (Mayo Clinic, no. 715857) suffering from chronic bilateral pyelonephritis with a severe secondary cystitis, who bled so furiously following cystoscopy that the hemoglobin fell from 90 to 42, and transfusion had to be performed. The reaction was associated with fever and a marked rise in the urea of the blood.

In addition, it must be remembered that there are reported in the literature many cases in which bleeding should have followed catheterization if this bleeding were due merely to the sudden withdrawal of residual urine. For example, Pinkham in 1875 withdrew by catheter 7,000 cc. of residual urine from a man of 67 who had had urinary difficulty for one month. Although he catheterized the patient daily for twenty days until his death, hematuria was not noted. Lund in 1885 withdrew at one sitting 13,960 cc. of urine from a woman of 40,

TABLE 6.—*Relation of the Lesion of the Kidney to Hematuria*

Lesion	Group Ia	Group Ib	Group IIa	Group IIb	Total
Acute pyelonephritis.....	8	6	3	3	20
Chronic pyelonephritis.....	2	1	0	5	8
Pyonephrosis.....	4	0	0	0	4
Total.....					32

who had had urinary difficulty for six weeks because of a retroflexed pregnant uterus. There was no hematuria, and the patient recovered. Corner and Bury withdrew 4,000 and 4,900 cc., respectively, under similar circumstances with similar results. Hamman in 1906 reported the case of a patient, aged 80, with a prostatic condition, with a history of one month's urinary difficulty, who was relieved of 7,800 cc. of urine without hematuria. He died four days later, still without bleeding.

It is difficult to understand why, if the emptying of the distended bladder *per se* leads to hematuria, this phenomenon should not occur uniformly when apparently ideal conditions are present. If, on the other hand, this bleeding is due to infection, its irregular occurrence can be understood easily since, as Cabot has said, "with two people equally exposed to infection, one may acquire it and one may not." The following cases present valuable evidence of the connection between infection and hematuria.

CASE 1 (University Hospital, no. 57593).—A male, aged 55, was admitted to the hospital in a state of coma due to meningitis secondary to acute otitis media. The stupor was of five and one-half hours' duration. Until its onset there had been no urinary symptoms. The bladder reached to the umbilicus. One thousand four hundred cubic centimeters of urine was withdrawn, following which there was an occasional red blood cell in the urine.

Death occurred ten and one-half hours after admission. At autopsy, there was moderate congestion of the vesical mucosa about the urethra.

CASE 2 (University Hospital, no. 58690).—A male, aged 72, gave a history of urinary difficulty of one year's duration. Prostatic hypertrophy was present. The residual urine amounted to 20 cc. It was sterile on culture. Suprapubic cystostomy was performed, and the urine obtained at this time was clear and sterile. The urine remained clear until seventy-two hours after operation, when there was a chill, the temperature rose to 102 F., and the urine became bloody. Culture now showed a streptococcus.

CASE 3 (University Hospital, no. 58940).—A male, aged 72, gave a history of difficult urination for several years and of nocturnal incontinence for three months. The bladder was palpable within a fingerbreadth of the umbilicus. The nonprotein nitrogen of the blood was 32 mg. per hundred cubic centimeters. The voided urine contained a few pus cells. Films made after the injection of iopax showed a moderate bilateral hydronephrosis.

Suprapubic cystotomy was performed under local anesthesia, and 1,500 cc. of clear urine was withdrawn. It was sterile on culture. The urine remained perfectly clear for twenty-four hours, and then became bloody. Culture then showed a mixed infection.

CASE 4 (University Hospital, no. 59072).—A man, aged 72 years, had had a urinary retention seven days before admission to the hospital for which he had been catheterized daily elsewhere. Thirty-six hours after the last catheterization, the bladder reached the umbilicus. The prostate was enlarged. The urine contained much pus and many bacteria. Catheterization yielded 1,400 cc. of urine at an initial pressure of 40 mm. of mercury. This urine and subsequent urines were free from microscopic or gross blood.

These cases present tangible evidence of the connection between infection and bleeding. In the first instance, bleeding did not follow the sudden withdrawal of 1,300 cc. of urine. In the second, gross hematuria did not occur until infection developed in a previously sterile urinary tract; there was but 20 cc. of residual urine. In the third patient, 1½ quarts (1,500 cc.) of urine was withdrawn and hematuria occurred, but not until twenty-four hours later. How can the latent period be satisfactorily accounted for except by the development of infection? The last patient's urinary tract was infected before admission, and the withdrawal of 1,500 cc. of residual urine had no effect except to make him more comfortable.

If mere reduction in pressure were responsible for renal bleeding, it should have occurred in the following cases:

CASE 5 (University Hospital, no. 52909).—A girl, aged 7, was in a serious condition as a result of a closed, infected hydronephrosis on the left. When the left kidney was opened for drainage under local anesthesia, 300 cc. of cloudy urine was obtained. It was under such pressure that the urine spurted 12 inches (30.48 cm.) into the air, yet bleeding did not follow.

CASE 6 (University Hospital, no. 552928).—A colored girl, aged 2 years, complained of a right-sided abdominal tumor. The right kidney was exposed under local anesthesia, and 1,300 cc. of clear urine was aspirated through a trocar; clear urine drained through the catheter that was left in the kidney for two weeks.

CASE 7 (University Hospital, no. 58982).—A woman, aged 57, had a bilateral infected hydronephrosis. Nephrostomy was performed on the right side under local anesthesia; when the kidney was punctured with a needle, urine escaped in a forceful jet. The urine that subsequently drained through the nephrostomy tube was but faintly tinged with blood for twenty-four hours.

Here, then, is incontrovertible evidence that bleeding from the kidney does not of necessity follow the sudden release of long-standing, increased, intrarenal tension.

To summarize the question of hematuria, one may say: (1) Spontaneous bleeding in prostatic hypertrophy is not uncommon; (2) it occurs in pyelonephritis without urinary retention; (3) it may originate from trauma (the prostatic and vesical congestion that are so common in urinary retention have already been discussed); (4) it is not entirely prevented by gradual emptying of the bladder; (5) in many instances the removal of tremendous quantities of urine under pressure both from the bladder and from the kidney has not provoked hematuria; (6) the experimental conditions necessary for the development of urinary infection are present in a patient with a prostatic condition (retention, trauma, bacteria); (7) in the instances of hematuria following catheterization in the literature, bacteriologic studies of the urine have not been made, and (8) in two cases of hematuria following sudden emptying of the bladder here reported, the hematuria was coincident with the appearance of bacteria in the urine; in each there was a definite latent period.

Surely then, one may hesitate to ascribe bleeding after catheterization to the specific effect of sudden relief of pressure alone, either in the bladder or in the kidneys.

To affirm that the fall of blood pressure already mentioned is the cause of death in such cases is not yet permissible. There is no evidence that urinary retention *per se* elevates the blood pressure. Shaw and Young in a large series of patients with prostatic obstructions with varying degrees of retention did not find the blood pressure elevated above the average for the age, a finding that is confirmed in this series (average of all cases 148 systolic and 74 diastolic, table 2). Further, while many observers have recorded definite falls in blood pressure after cystotomy and after catheterization, in very few instances has the pressure fallen to shock levels, as in the cases of Shaw and Young, in which recovery ensued. The fall was heralded, in the case described by Shaw and Young in detail, by a rigor, a fact that is of interest in view of Elfving's observation of falling blood pressure in acute pyelonephritis. A case that illustrates this point is worth recording:

CASE 8 (University Hospital, no. 50940).—A man, aged 50, had a urethral stricture without retention of urine. Following dilatation of the stricture, there was a rigor; the blood pressure two hours later could not be read; the pulse was rapid and thready; almost complete anuria obtained for twelve hours. Following



the intravenous administration of saline, the pressure rose to normal; the fever subsided; the anuria disappeared. Yet "decompression" could not have occurred.

Also, one author who recorded a drop in blood pressure after cystotomy for retention used cocaine as an anesthetic (Pilcher). It is to be considered, too, that any operation on patients of the type usually suffering from urinary retention is likely to lead to a fall in blood pressure, since these people are in a state peculiarly subject to so-called "surgical shock."

In the six cases here recorded in which large amounts of residual urine were removed abruptly, the blood pressure did not change.

It is permissible to conclude that there are three types of blood pressure declines in these cases; (1) the fall due to a relaxation of the nervous tension due to vain attempts to urinate and to admission to an institution; (2) that due to the toxemia of acute pyelonephritis, and (3) that resulting from so-called surgical shock. There is thus far no conclusive evidence that the release of heightened tension in the urinary tract *per se* can reduce the blood pressure. Further, Elfving has repeatedly noted blood pressure levels below the average in patients with prostatic conditions with "ischuria paradoxa" (overflow incontinence) before any manipulation was carried out; nor did any decrease occur on catheterization in his cases.

On turning to the pathologic evidence, one finds further support for the conclusions so far reached. Seventy of the seventy-one patients had infectious changes in the kidneys. In 73.2 per cent these changes were acute. On reviewing those instances in which acute lesions were lacking, one finds hopeless impairment of the kidney function before catheterization in most instances in which renal insufficiency was prominent after catheterization. The patients who died without renal insufficiency succumbed to extrarenal infectious processes in four of nine cases.

In other words, of seventy-one patients who died after catheterization in the presence of residual urine, death was due to frank infection in all but five; three of these fatalities were due to pulmonary embolism, in which bacteria are implicated by most observers.

It has been impossible to identify a characteristic lesion that can be attributed to sudden drainage of the urinary tract *per se*.

The deaths that the older writers ascribed to syncope in the absence of complete postmortem studies have their counterparts in this series in the three patients who succumbed to pulmonary embolism and in a fourth who had coronary thrombosis.

There have been appended to the case records those of two patients who died of renal insufficiency secondary to prostatic hypertrophy, who had not been subjected to instrumentation (cases 30 and 66). They presented lesions in every way similar to those seen in the main group.

The separate study of the patients who died within a week after catheterization did not reveal any essential difference from that of those who succumbed more slowly. As might have been expected, they represented poorer risks; they were older and had slightly higher average blood pressures than the whole group; their kidney function was poorer, and a larger percentage (70) failed to show acute changes in the kidneys.

Separation of those whose entire residual urine was removed at once from those whose bladders were emptied gradually did not yield significant differences. As has been pointed out, the kidney function was not adequately studied in a sufficient number to permit comparison. Partial suppression of the urine occurred in a higher percentage after sudden emptying than after gradual decompression; unfortunately, incomplete records and the small number of cases prevent the drawing of conclusions. The striking similarity of the kidney lesions in the two groups certainly militates against the idea that the manner in which the bladder is emptied is of any significance in the lethal outcome.

#### SUMMARY

1. It is an accepted theory that the sudden removal of residual urine that has been present for any considerable period in prostatic hypertrophy is dangerous.

2. The presence of partial urinary retention leads to an increased tension in the bladder. This in turn causes an increase in the pressure in the kidney pelves, which leads to hydronephrotic atrophy.

3. The presence of urinary retention has been shown experimentally to be a potent factor in increasing the susceptibility of the urinary tract to infection.

4. Mechanical trauma (catheter) has been shown to have a similar influence.

5. It has been suggested that the sudden withdrawal of residual urine reduces the pressure in the urinary tract and so leads to congestion, hematuria and interference with the kidney function with urinary suppression apart from any infectious process.

6. Acute pyelonephritis and its complications are capable of producing all of the phenomena seen after sudden emptying of the distended bladder.

7. Sixty-eight of the sixty-nine patients dying after catheterization and here studied showed lesions of an infectious character in the kidneys.

8. Eighty and two-tenths per cent of these patients manifested clinical uremia before death.

9. Sudden death occurred four times; it was due twice to pulmonary embolism and once to coronary thrombosis.

10. No lesions that were attributed to sudden emptying of the bladder without infection could be found.

11. Infection could be assigned as the cause of death in all but one of the patients.

#### CONCLUSIONS

1. Many patients with chronic incomplete retention of the urine undoubtedly die as a direct result of catheterization.

2. That death may result solely from the mechanical effect of this sudden emptying of the bladder has been claimed repeatedly, but has not been proved.

3. Patients who die as a result of catheterization die of infection in the majority of instances.

4. Whether there is any connection between the rate at which the bladder is emptied and the fatal issue (infection) is a moot point.

5. It seems more likely that the mere introduction of infection into a urinary tract prepared by long-standing obstruction (and quite independent of the rate at which the bladder is emptied) is the exciting cause of the fatal issue.

6. The value of gradual emptying of the chronically distended bladder is therefore open to question, although the complete abandonment of this procedure is perhaps not justified.

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NOTE.—Since submitting this article for publication, my attention has been called to an important contribution to the literature on sudden decompression of the bladder. Brecher and Chwalla (Neues zur Therapie nebst Untersuchungen über die Entlastungsreaktion und die Diurese bei chronischer Harnstauung, *Ztschr. f. urol. Chir.* **31**:266, 1931) have reported, after a study of three hundred cases of urinary retention, eighty of which had one liter or more of residual urine, that no untoward reaction was encountered from sudden emptying of the bladder. They found that bleeding was as frequent and as profuse with gradual as with sudden emptying, and that the fall in blood pressure with sudden emptying was never alarming. They concluded that the indication is for prompt and complete emptying, good drainage, scrupulous asepsis and a high intake of fluid. They expressed the belief that gradual emptying is more dangerous than sudden emptying.

# IMPROVED THYROIDECTOMY TECHNIC

WITH SPECIAL REFERENCE TO THE CONSIDERATION OF THE  
RESULTS OF ELIMINATING DRAINAGE IN A SERIES  
OF 1,200 CASES

JOSEPH L. DECOURCY, M.D.

CINCINNATI

Drainage of the wound in thyroidectomy still seems to play a prominent part in thyroid surgery in many clinics. Some operators are still of the opinion that the serum following thyroidectomy is toxic and should be drained away. Others feel that drainage will develop whether or not a drain is used.

The results at the DeCourcy Clinic, however, in a series of 1,200 thyroidectomies during the past three years have caused us to regard drainage as unnecessary and even harmful. In our experience, the preoperative preparation of the patient through iodine medication and the resulting simplification of operative technic are factors of import in the prevention of the accumulation of serum. Serum has collected in only a very small percentage of our cases, and drainage has not been indicated.

It will be of pertinent interest to discuss the practices that have found favor in our clinic, and because of which, in our opinion, drainage is a procedure which will best serve the patient by its omission.

In this paper I do not contemplate the difficult subject of the diagnosis of thyrotoxicosis. In simple goiter, operation will be indicated when the goiter by reason of its size and position becomes oppressive on the trachea. There are those who agree with Short,<sup>1</sup> who has observed that all patients with toxic adenoma of the thyroid and all patients with exophthalmic goiter of a year's duration should be operated on. He has found good reason for operating in early cases as well.

At the Belgian Congress of Otorhinolaryngology, van den Wildenberg,<sup>2</sup> commenting on the failure of radiotherapy, reached the conclusion that the lamentable thing about radiotherapeutic treatment for exophthalmic goiter, whether specific or symptomatic, is that it does not accomplish its purpose, entails a great loss of time, exhibits but temporary benefit and may seriously damage the operative field.

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From the Department of Surgery, DeCourcy Clinic.

1. Short, A. R.: *Five Years of Surgery in Exophthalmic Goiter*, Bristol Med.-Chir. J. **47**:185, 1930.

2. van den Wildenberg, cited in Belgium letter, J. A. M. A. **95**:741 (Sept. 6) 1930.

Though the medical treatment of thyrotoxicosis has recently won warm adherents in some quarters, conclusive reports are few and the series of cases observed small in number. It has been our experience that the successful treatment of thyrotoxicosis is surgical. In mild cases, operative risk is slight. In the more grave cases, technic has been so simplified as to reduce risk markedly and to lower mortality. With newer methods of preoperative preparation and postoperative care, we now operate successfully in the presence of pregnancy, diabetes and tuberculosis. Subtotal removal of the offending thyroid frequently reduces glycosuria and alleviates the tuberculous exacerbation.

From his series of 6,700 goiter operations, Lahey<sup>3</sup> deduced that there are practically no thyrocardiac patients in whom the decompensation is due to a superimposed thyroidism who cannot be operated on, when measures are utilized to prepare the patient and avert thyroid crisis. It has been my experience in a small series<sup>4</sup> that mental patients with hyperplastic goiter have undergone complete mental recovery without recurrence, after thyroidectomy. Even the patients with extremely severe thyrotoxicosis, with marked emaciation, vomiting, prostration and acidosis, may be brought to a state of operability. Crile,<sup>5</sup> in an analysis of 20,000 cases, has reckoned that the number of patients who cannot be restored to operability is only 0.2 per cent.

#### THE INDISPENSABLE RÔLE OF IODINE

It is now almost ten years since the preoperative use of iodine was instituted. Before that time, iodine was used in the treatment for goiter in a haphazard way, and its effect on the gland was little understood. It is now known that its use before operation converts the hyperplastic gland, partially at least, to the colloid state and permits an easier and more thorough removal. It has lessened the hazard of operation on this type of goiter considerably.

Prior to Plummer's revolutionary introduction of iodine in thyrotoxicosis at the Mayo Clinic in 1922, operations for goiter required far greater judgment and ingenuity than are necessary at the present

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3. Lahey, F. H.: Deductions from 6,700 Goiter Operations, *New England J. Med.* **200**:909, 1929.

4. DeCourcy, J. L.: Thyroidectomy in Mentally Disturbed with Exophthalmic Goiter: Report of Twelve Cases in Which Psychosis Was Relieved by Operation, *Am. J. Surg.* **6**:21, 1929; Thyroidectomy in Mentally Disturbed Patients with Exophthalmic Goiter, *J. Nerv. & Ment. Dis.* **68**:384, 1928; Toxic Goiter and Mental Disease: Relief of Psychosis in Thyrotoxic Patients by Thyroidectomy, *Arch. Surg.* **17**:296 (Aug.) 1928.

5. Crile, G. W.: A Clinical Analysis of 20,000 Operations on the Thyroid Gland with Special Reference to End Results, *Proc. Interstate Post-Grad. M. A. North America*, 1929, p. 393.



time. "Step" operations were then in vogue, and it was not unusual to commit a patient to six or seven ordeals, consisting of from two to four ligations, partial removals, leaving the wound open until reaction subsided, etc. At the present time the operation of two, four, six or eight stages is a rarity and required only in the very exceptional case.

The independent studies of Neisser, Loewy and Zondek in Germany confirmed the results of Plummer. In present practice, the efficacy of the drug is fully established, and iodine is for the most part in routine use to prepare patients for operation. Iodine administration enables the physician to operate during the period of most marked improvement, for observation has demonstrated that, with too long a course, the beneficial effects disappear. With iodine, in our series of cases we have been able to dispense with preliminary ligation entirely.

We have found it of advantage to keep the patient in bed after admission to the clinic. We urge the patient to eat very heartily and partake fully of fluids. In severe cases, we restore water equilibrium by subcutaneous infusion. Preliminary blood transfusion may be a necessary prophylactic course, as well as digitalization, if there is a failing myocardium, and sedation to control nervous excitement.

Lahey<sup>3</sup> has found that the preoperative employment of iodine has practically eliminated preliminary pole ligations. In an earlier paper, Clute<sup>6</sup> and his associates at the Lahey Clinic in Boston asserted that it was their practice with patients not dangerously ill to wait until after the first metabolic test before giving compound solution of iodine. In severely toxic patients it was their custom to administer the solution immediately, without waiting for metabolism tests. In the latter type of case they gave from 50 to 100 minims (3 to 6 cc.) within the first twenty-four hours after admission, in divided doses of 5 or 10 minims by mouth or rectally. In the less dangerously ill patients, the dosage was 10 minims of the solution three times a day, continued during the preoperative period and for several days after operation. If a severe postoperative reaction was anticipated, the dose was doubled on the day preceding and the day of operation. They have found it essential to continue the drug through the whole operative period in order to avoid reactions.

In some clinics doses of 10 minims once a day or in divided doses are given for six or eight weeks postoperatively. The method at the DeCourcy Clinic has been explained in one of my earlier papers.<sup>7</sup> In

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6. Clute, H. M.: Effect of Compound Solution of Iodine and Rest in Surgery of Exophthalmic Goiter, *J. A. M. A.* **86**:105 (Jan. 9) 1926.

7. DeCourcy, J. L.: Surgical Goiter: How Modern Methods of Preparation, Anesthesia and Technic Have Improved the Surgical Results and Reduced Mortality to an Almost Negligible Percentage, *Am. J. Surg.* **10**:483, 1930.

general, the quantity of iodine necessary for maximum benefit must be estimated from the size of the gland and degree of abnormality present. Between courses of iodine there should be an interval of at least a month. Complete involution of the gland will indicate that sufficient iodine has been given. We administer 10 drops of compound solution of iodine three times a day for from two to four weeks preceding operation.

In severely toxic patients, in the absence of irregularity of heart beat or decompensation, three doses of 30 minims each of standardized tincture of digitalis are given at intervals of eight hours. In the presence of cardiac arrhythmia, 10 drops of tincture of digitalis are administered three times daily until compensation is restored. We discontinue the administration of digitalis about five days before operation and resume it immediately afterward.

The immediate effects of iodine therapy are relaxation of nervous tension, fall in basal metabolism of from two to four points daily and lowering of the pulse rate. The patient sleeps better and eats better. His weight increases, and prostration is alleviated. There is, however, a small percentage of patients who experience no benefit from iodine.

With the persistence of iodine therapy through the postoperative period, we have found that thyrotoxic crises are markedly diminished in both number and severity. If necessary, the iodine may be administered by rectum. Postoperatively, dehydration must be counteracted. Dextrose administered intravenously during the crisis will alleviate acute acidosis. Foster<sup>8</sup> advised:

Not less than 100 grams of glucose is required during twenty-four hours to prevent acidosis under the conditions of a thyrotoxic crisis. This amount is conveniently given by using a 50 per cent glucose solution, 20 grams being administered intravenously every four hours for five or six doses during twenty-four hours.

#### ANESTHESIA AN IMPORTANT FACTOR IN THE REDUCTION OF MORTALITY

I have made the declaration in a previous paper<sup>9</sup> that, next in importance to preoperative use of compound solution of iodine and simplification of surgical technic, choice of a safe anesthesia ranks as a decisive factor in reduction of mortality. It is generally accepted that profound general anesthesia is dangerous and conducive to postoperative crises. In many instances the choice of the anesthetic must

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8. Foster, N. B.: Thyrotoxicosis, in Nelson's Loose Leaf Living Medicine, New York, Thomas Nelson & Sons, 1928, vol. 3.

9. DeCourcy, J. L.: Thyroidectomy Anesthesia: A Study of Different Methods of Anesthesia Used in 4,000 Goiter Operations, *Am. J. Surg.* 5:170, 1928.

depend on the individuality of the case. The anesthetist must be conversant with the use of local and general anesthesia as well, and equipped to change from one to the other as may be necessary.

At the DeCourcy Clinic, in approximately 6,000 goiter operations during the past eleven years, we have for the past six years used nitrous oxide and oxygen anesthesia as a routine procedure. In our experience it is the anesthesia of choice. Our present preference for nitrous oxide and oxygen is based on our experience with several other methods.

We have found that, with nitrous oxide and oxygen, there is a minimum of postoperative nausea and hemorrhage. Under this light anesthesia, any nerve trauma during operation can be detected by the exhibition of a change in respiratory rate and characteristic modification of inspiration. On immediate removal of nerve pressure or repair of nerve damage will depend in part the satisfactory after-course of the patient. Under nitrous oxide and oxygen anesthesia, the administration of pure oxygen under direct pressure will alleviate too profound a narcosis.

The aim in nitrous oxide and oxygen anesthesia should be to maintain unconsciousness and at the same time preserve the natural "pink" of the skin. A change in the natural color of the skin will indicate cyanosis. Under this method of anesthesia, such a crisis may be quickly averted, however, by administering oxygen. Conversely, it is but the work of a moment to induce deeper narcosis should the procedure of the operation demand it. The usual patient returns to consciousness under this mode of anesthesia before he leaves the table.

Other forms of anesthesia which have found favor at various clinics are local anesthesia, local anesthesia together with nitrous oxide and oxygen, local anesthesia together with either nitrous oxide or light ethylene inhalation, ethylene administration and rectal anesthesia. Block anesthesia has been utilized as well. Frequently anesthesia for thyroidectomy is still induced by ether and chloroform; it is my experience that other methods are preferable by far.

Parker,<sup>10</sup> who recently prepared a paper on the routine procedure in thyroidectomy at the surgical clinic of the University of Heidelberg, asserted that all operations there, except on the occasional highly toxic patient, are performed under local anesthesia. About 20 per cent of the entire population of the Middle Rhine District is affected with goiter, and about 250 patients are operated on annually. From his observation at this clinic, Parker was convinced of the superiority of local anesthesia with procaine and epinephrine hydrochloride. The

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10. Parker, M. L.: *Technique of Thyroidectomy*, Surg., Gynec. & Obst. 52: 238, 1931.

epinephrine prolongs the duration of the anesthesia two or three hours. He observed that the technic of this anesthesia is simple, renders a comparatively bloodless field and avoids damage to the heart, lungs and compressed trachea. An important consideration, he observed, is the fact that the operator can converse with the patient and quickly detect any change in the patient's voice indicating operative injury to the recurrent laryngeal nerve. At that clinic, general anesthesia is employed in less than 1 per cent of goiter operations.

I, personally, have operated on 500 patients under local anesthesia, but at the point when the gland is raised up have many times had to give ether by the open drop method to induce narcosis when the patient became panicky because of a feeling of strangulation. The patient suffers psychic shock, and the time required for operation is unduly long. Also, postoperative nausea and vomiting are aggravated.

Local infiltration, together with nitrous oxide and oxygen, is the method favored by Crile. Crile's method of anoci-association has been likened by Babcock to "stealing the patient's gland without his knowledge." He describes the procedure as follows: The patient is not told when the operation is to be performed. Daily he receives hypodermic injections, inhalations of air and, perhaps, a little nitrous oxide. The patient wears a bandage about the neck, and becomes accustomed to these daily routines. On the appointed day a hypodermic of morphine is substituted for the previous injections of salt solution, nitrous oxide is given to effect, and the local anesthetic injected. The operation is carried on preferably in the patient's own room.

It is my experience that anesthesia by nitrous oxide and oxygen is not a simple procedure, but requires a high degree of patience and skill. It is, however, a thoroughly satisfactory anesthesia with respect to the comfort of the patient and end-results.

#### TECHNIC TO AVOID UNDESIRABLE RESULTS

Successful thyroidectomy must anticipate the possibility of, and avoid by its choice of routines, primary or secondary hemorrhage, surgical shock, postoperative collapse of the trachea, injury to or accidental removal of the parathyroid glands, trauma to the recurrent laryngeal nerves and air embolism.

Only in the very large hyperplastic thyroids have we resorted to a two-stage operation, by performing single partial lobectomy and completing the operation from twenty-four to forty-eight hours later. Our usual technic consists of bilateral subtotal thyroidectomy including removal of the isthmus and suture of the sternothyroid muscle to the pretracheal fascia on each side of the trachea with fine catgut.

The transverse line of incision is so placed as to follow the line of a normal wrinkle, in women where a necklace will cover the resulting

linear scar. Tyler has recently suggested a simple device for marking the line for incision. With a trial necklace in place, he outlines the proposed incision with bismuth violet. When the dye is dried, he paints the field with dilute tincture of iodine, which does not obliterate the demarcation.

The general procedure is to separate the ribbon muscles in the midline to remove small glands. For large goiters, the strap muscles will need to be cut transversely to expose the thyroid sufficiently for excision. The isthmus is then divided and one lobe delivered, leaving a thin section of gland to insure keeping the recurrent nerve and the parathyroids intact. The opposite half is then delivered.

It is our custom rigorously to observe careful ligation of every blood vessel as it is exposed to avoid air embolism and reduce hemorrhage. Preliminary ligation of the superior thyroid arteries insures excellent hemostasis and reduces the danger of postoperative hemorrhage. Parker ligates the superior thyroid artery with three ligatures. Only four fifths or five sixths of the gland should be removed, and the portion remaining must definitely be that section which will protect the recurrent nerve and the parathyroids, to avoid postoperative tetany. Parker described the amount of good thyroid tissue necessary for body function as about the size of a hazelnut on each side.

In our experience the suture of the sternothyroid muscle to the pre-tracheal fascia on each side of the trachea has appeared to decrease hemorrhage, possibly owing to the hemostatic action of the muscle over the denuded surface of the gland. There were no postoperative hemorrhages in our entire series.

Any damage to the parathyroid glands will result in postoperative tetany. When a parathyroid gland had been accidentally removed, Lahey successfully overcame the accident by immediately replanting the dissected gland. Other operators have successfully transplanted parathyroid glands from persons with the same blood grouping. In operating it is well to avoid the removal of any fatlike processes, as the exact position of the parathyroids cannot always be depended on. One of the latter day remedies of great value in tetany is administration of the parathyroid extract Collip.

Under nitrous oxide and oxygen anesthesia, injury to the recurrent laryngeal nerve may be detected by a change in the texture of the breathing and steps instituted to remove or repair the injury. If a clamp or oppressive ligature is the cause, it must immediately be removed. Should the nerve be cut accidentally, it should be sutured.

Although gentleness of technic will avoid injury to the trachea, certain conditions of tracheal collapse are unavoidable, such as collapse occasioned by atrophied tissue due to long standing pressure from a

large thyroid. It is a serious complication, and fatal termination can be avoided only by immediate tracheotomy. At best, the prognosis is doubtful.

#### IS POSTOPERATIVE DRAINAGE NECESSARY?

Babcock observes that if there is no oozing drainage is not required. But many operators still feel that provision for drainage is indispensable to prevent postoperative toxicosis and accident.

For the past three years we have not used a drain except in the very large substernal type of goiter in which a large cavity remains. In our series of 1,200 cases during this period of time we have found it advisable to insert a drain possibly in twelve cases, or 1 per cent. The two-stage operation was done only in the very large hyperplastic glands, and here the wound was completely sealed between stages.

The results with bilateral subtotal thyroidectomy, together with suture of the sternothyroid muscle to the pretracheal fascia on each side, have caused us to conclude that not only may drainage be omitted, but it is to the best interests of the patient to omit it. In comparison with cases in which drainage is used, the postoperative reaction without drainage has certainly not been greater. Possibly, it is less.

It is true that in about one of every ten cases some serum may collect. However, frequently this serum will be absorbed without puncture. When we have decided that puncture was advisable, we have found that usually only one puncture has been required. We have found that if care is used in closure and minute attention given to hemostasis during operation, drainage will not be necessary. When formerly we were accustomed to employ drainage, it was not unusual to have cases drain for from four to six weeks, and even longer.

Without drainage we have found that postoperative care is reduced to a minimum, and the resulting scar is negligible.

Postoperatively, complete rest, transfusion in the presence of extreme prostration, the usual measures to prevent or relieve dehydration and shock, digitalis for auricular fibrillation, iodine and quinine hydrobromide for thyrotoxicosis, together with refrigeration should crisis arise, parathyroid extract Collip and calcium lactate in the event of tetany, and sedatives are the usual measures that favor progressive and uneventful recovery.

#### A WORD REGARDING MORTALITY STATISTICS

Recent papers on thyroidectomy are for the most part unanimous in acclaiming the extraordinary reductions that have been accomplished in mortality percentages. In a previous paper,<sup>11</sup> I was able to

11. DeCourcy, J. L.: The Mortality of Operations upon the Thyroid Gland, with an Analysis of 388 Operations Performed During 1927, *Ann. Surg.* **89**:207, 1929.

deduce from a comparative study of reports from the clinics that the mortality following thyroid operations has been reduced to approximately 1 per cent. In my more recent contribution,<sup>7</sup> I was able to report that mortality at the DeCourcy Clinic had been reduced, for the year of 1929, to less than 0.25 per cent. Parker reported that at the surgical clinic at the University of Heidelberg, mortality is almost unknown, being less than 0.5 per cent.

A word of warning, however, has been sounded by Beckman:<sup>12</sup>

In more recent years, the improvement in surgical procedure made possible by preliminary iodine and rest is greater even than appears in the above table [table omitted herewith]; several clinics now operate more than 80 per cent of their cases as single-stage subtotal thyroidectomies. In a few specialized clinics, by reason of skilful surgery plus organized team-work . . . the operative mortality has been reduced below 3 per cent; but the reader will do well to note Foster's recent statement that in general hospitals, where this perfected coördination is not possible, the mortality is still about 15 per cent. [For Foster's statement, see footnote 10.]

To maintain a low mortality percentage, it will be well for the surgeon to recall with Clute<sup>13</sup> that most of the unexpected mortalities arise in patients of 40 years and over who weigh around 100 pounds (45.4 Kg.) or have suffered great loss of weight, or patients who have had well marked hyperthyroidism for more than a year. It is Clute's observation that, in the severe surgical risks, thyroidectomy should be divided into stages. From Beckman's figures it would appear that conservatism must still govern thyroidectomy procedures if it is desired to maintain the tremendous advance that has been accomplished.

#### CONCLUSIONS

In a series of 1,200 thyroidectomies in the past three years, we have employed preoperative preparation with iodine. Our usual technic consists of bilateral subtotal excision. Our procedures have made drainage necessary in only approximately 1 per cent of cases. It is our observation that drainage is usually unnecessary and even harmful.

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12. Beckman, H.: *Treatment in General Practice*, Philadelphia, W. B. Saunders Company, 1930, p. 609.

13. Clute, H. M.: *The Operative Mortality in Hyperthyroidism*, J. A. M. A. 95:392 (Nov. 22) 1930.

# GASTRIC ACIDITY WITH SPECIAL REFERENCE TO THE PARS PYLORICA AND PYLORIC MUCOSA

AN EXPERIMENTAL STUDY

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## GASTRIC ACIDITY FOLLOWING RESECTION OF THE PARS PYLORICA

The cause of the lowered gastric acidity following gastric resection on the human being has been intensively studied, and although many hypotheses have been offered in explanation, as yet none has been satisfactory. Many observers state that the lowered acidity results from loss of the pars pylorica, which they credit with great significance in the regulation of gastric secretion. Our investigations, which were conducted entirely on dogs, were undertaken with the purpose of attempting to evaluate this supposed function of the pyloric mucosa more accurately.

Few, if any, surgeons still disagree with anatomists by stating that acid-forming glands are removed when only the pars pylorica is resected;<sup>1</sup> likewise, few accept the existence of a "nerve center" in the region of the incisura supposedly essential for normal gastric secretion.<sup>2</sup> The reason often advanced for the decreased acidity following resection of the pyloric antrum has been that in this region "the major part of gastric secretion is initiated."<sup>3</sup> This opinion, widely accepted since Edkins'<sup>4</sup> original paper in 1906, despite lack of any actual proof to substantiate such a view, entirely disregards the psychic, local, mechanical, nervous and intestinal phases of gastric secretion which are definitely known to exist.

*Method.*—Observations were made on the gastric acidity of four dogs. The normal gastric response to a test meal (80 Gm. of ground meat and 250 cc. of water) was first determined for each animal, which was pre-

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From the Division of Experimental Surgery and Pathology, the Mayo Foundation.

1. Deaver, J. B., and Reimann, S. P.: Subtotal Gastrectomy, J. A. M. A. **85**:1619 (Nov. 21) 1925.

2. Crohn, B. B.: Chemism of Stomach After Operation, S. Clin. North America **5**:53 (Feb.) 1925.

3. Klein, Eugene: Gastric Secretion After Partial Gastrectomy, J. A. M. A. **89**:1235 (Oct. 8) 1927.

4. Edkins, J. S.: The Chemical Mechanism of Gastric Secretion, J. Physiol. **34**:133, 1906.



viously trained over a period of weeks to swallow the stomach tube, during which time preliminary observations were made. Similar gastric analyses were made following the subcutaneous injection of 1 mg. of histamine. Specimens were withdrawn at fifteen-minute intervals until the stomach was empty, and they were tested for free and total hydrochloric acid and hydrogen-ion concentration in each instance, with the use of a quinhydrone electrode for the latter. Following at least three

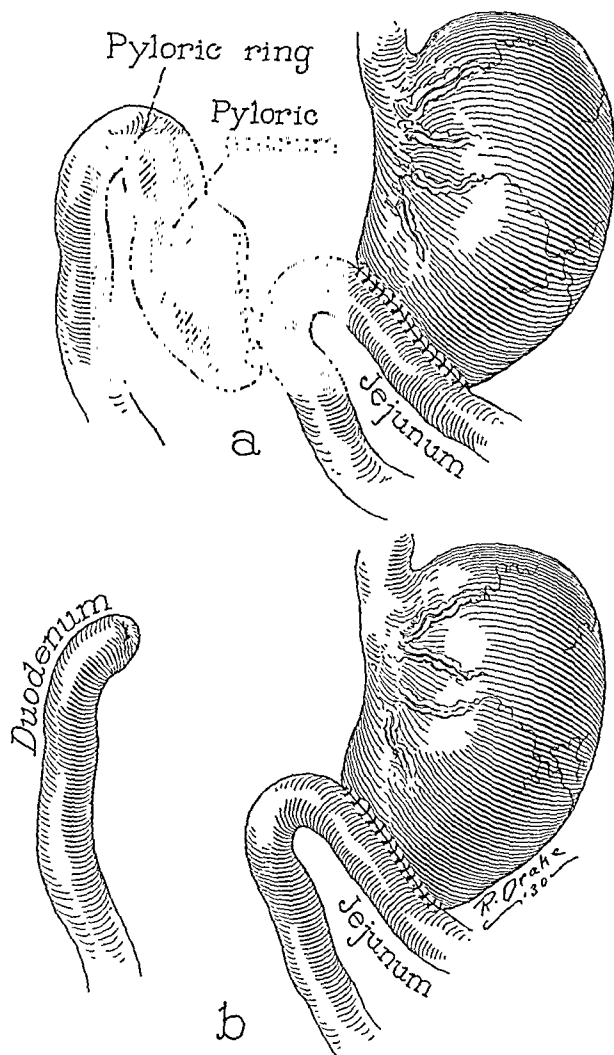


Fig. 1.—In *a*, is shown the first procedure; in *b*, removal of the pyloric antrum.

successive curves which coincided closely, each animal was subjected to the first operation. All operative procedures were performed under ether anesthesia.

At this time the stomach was sectioned at the so-called prepyloric sphincter, the pyloric end was inverted and the fundic portion was anastomosed end-to-side to the first free loop of jejunum. Similar observations again were made on gastric acidity, starting a month or more after operation. After standard curves were again obtained, the

second operation was performed, at which time the pyloric portion of the stomach, previously disconnected from the fundus, was excised. The portion removed averaged 5.5 cm. along the lesser curvature and 7 cm. along the greater curvature (fig. 1). Gastric analyses were now repeated. More than 1,000 different specimens were analyzed for each dog.

*Results.*—The results were largely of the negative type. In no instance was there any appreciable alteration in the free hydrochloric acid following either the first or the second operation. In three of the four dogs there was a moderate decrease in the total acidity following

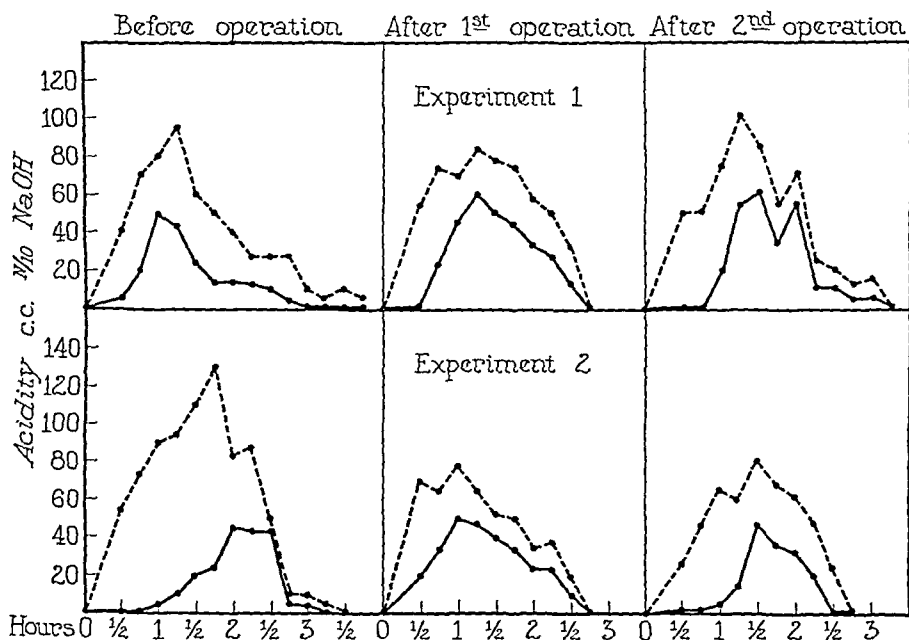


Fig. 2.—The free (solid line) and total (dotted line) acidity is shown in response to a test meal given to two dogs (experiments 1 and 2) before operation, following the first operation and following the second operation. In the first experiment, gastric acidity was practically unaffected by operation, and in the second experiment total acidity was reduced after the first operation and remained unchanged after the second operation.

the first operation (isolation of the pars pylorica from the fundus). This remained unchanged following resection of the pyloric antrum. In other words, extirpation of the pars pylorica did not cause more alteration in gastric acidity than mere isolation of this region from the fundus (figs. 2 and 3). The emptying time was shortened by the first operation and unaffected by the pyloric resection. Microscopic sections of the pyloric antrum disclosed a normal appearing mucosa and gastric wall in each instance.

*Comment.*—We did not consider that the acid values had changed following operation if the maximal postoperative values equaled the maximal preoperative values. Owing to many extraneous factors influencing gastric reaction, general average curves were not taken as the most accurate means of comparison. The pyloric mucosa of the dog apparently is not a necessary or an important factor in normal gastric acidity. This does not necessarily imply that a humoral agent might not originate in the pyloric mucosa. Our investigations, as will be shown, suggest that a true humoral stimulant of gastric secretion is not initiated in this region. It is not denied, however, that in the intact animal, with the nerve supply to the stomach undisturbed, the pyloric mucosa may indirectly play a part in the production of gastric acidity.

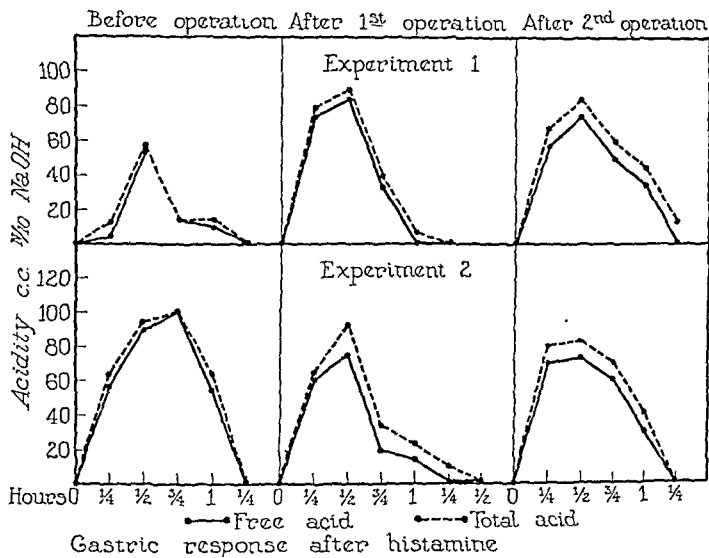


Fig. 3.—Free and total acidity following the injection of 1 mg. of histamine into two dogs (experiments 1 and 2) before operation and after the first and second operation. Practically no change was caused by operation.

In contrast with the ever-present tendency to offer a single explanation for a physiologic phenomenon, in this case there seem to be at least four factors contributing in varying degrees to the lowered acidity following partial gastric resection: (1) Frequently more than the pars pylorica is resected and thereby acid-forming glands are removed; (2) dilution and perhaps some neutralization with excessive regurgitation of duodenal juices takes place; (3) since food leaves the stomach sooner, it stimulates gastric secretion for a shorter period and the acid is not allowed to accumulate in the stomach for such a long period, and (4) food reaching the upper part of the intestine less completely digested than normally may not initiate the normal amount of stimulation during the intestinal phase of gastric secretion.

EVALUATION OF THE PYLORIC MUCOSA IN THE HUMORAL  
STIMULATION OF GASTRIC SECRETION

Despite many investigations of the humoral phase of gastric secretion since Edkins' original paper in 1906, the exact rôle of the pyloric mucosa in this mechanism is still disputed. Ivy and Farrell<sup>5</sup> and Lim and Necheles<sup>6</sup> have demonstrated that some humoral stimulation may occur. However, three fundamental questions remain unanswered: From what part or parts of the gastro-intestinal tract does this humoral agent arise? How important is this factor in normal digestion? Is this agent primarily secretagogic or hormonal? Although there is no direct evidence regarding its significance in normal digestion, a review of the work on this subject gives one the impression that it has not been proved a factor of great importance. Whether it is primarily secretagogic or hormonal remains unknown. The purpose of this investigation was an attempt to determine the part, if any, that the pyloric mucosa plays in the humoral stimulation of gastric secretion. Dogs were used exclusively.

In contrast with current opinion, there are numerous observations in the literature suggesting that humoral stimulation of gastric secretion does not originate from activity of the pyloric mucosa. Sawitsch and Zeliony,<sup>7</sup> using dogs having an isolated pyloric pouch with nerves intact and a fistula in the fundus of the stomach, found increased acidity in the fundus when certain solutions were placed in the pyloric pouch. This response was absent following the administration of atropine or the application of cocaine locally in the fundic mucosa. Ivy and Whitlow,<sup>8</sup> using dogs with an isolated pyloric pouch and a Pavlov pouch, could not demonstrate any secretory effect on the Pavlov pouch regardless of what they placed in the pyloric pouch. Later Lim, Ivy and McCarthy,<sup>9</sup> using dogs prepared similarly to those of Sawitsch and Zeliony, obtained results confirming the work of these authors. They then concluded that the Pavlov pouch is more refractive than the normal stomach. However, if a true humoral agent were formed in the pars pylorica, it should stimulate secretion in a Pavlov pouch.

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5. Ivy, A. C., and Farrell, J. I.: The Proof of a Humoral Mechanism: A New Procedure for the Study of Gastric Physiology, *Am. J. Physiol.* **74**:639 (Nov.) 1925.

6. Lim, R. K. S., and Necheles, H.: Demonstration of a Gastric Secretory Excitant in Circulating Blood by Vivo-Dialysis, *Proc. Soc. Exper. Biol. & Med.* **24**:197, 1926.

7. Sawitsch, W., and Zeliony, G.: Zur Physiologie des Pylorus, *Arch. f. d. ges. Physiol.* **150**:128, 1913.

8. Ivy, A. C., and Whitlow, J. E.: The Gastrin Theory Put to Physiological Test, *Am. J. Physiol.* **60**:578, 1922.

9. Lim, R. K. S.; Ivy, A. C., and McCarthy, J. E.: Contributions to the Physiology of Gastric Secretion: I. Gastric Secretion by Local (Mechanical and Chemical) Stimulation, *Quart. J. Exper. Physiol.* **15**:13, 1925.

The humoral secretion demonstrated by Ivy and Farrell in dogs with totally transplanted fundic pouches also suggests that the pyloric mucosa is not the site of formation of the humoral agent since no effect was noted for from two to six hours following a meal. This suggests that the humoral agent bears a relationship to the intestinal phase of gastric secretion. Portis and Portis<sup>10</sup> found, following surgical removal of the pars pylorica in dogs having a Pavlov pouch, that the secretion of the pouch responded in the same manner to test meals when the pyloric mucosa was absent.

*Method.*—In this work two series of dogs were studied. In the first series, an isolated pyloric pouch and a fundic fistula were made. At the first operation two fistulas were placed in the stomach according to the technic described by Mann and Bollman,<sup>11</sup> one in the fundus and the other in the pars pylorica. Several weeks later, the stomach was completely sectioned at the so-called prepyloric sphincter (averaging 4.5 cm. on the lesser curvature and 6.5 cm. on the greater curvature from the pyloric ring). An end-to-end gastrojejunostomy was done; the pylorus was severed, and both ends were inverted. The pyloric pouch so formed received few, if any, vagal fibers; however, its sympathetic supply was less disturbed (fig. 4).

In the second series of dogs, an isolated pyloric pouch and also a totally transplanted fundic pouch were formed. At the first operation a fundic pouch was formed and placed in the subcutaneous tissue of the abdominal wall. About a month or six weeks later a completely isolated pyloric pouch was formed, gastro-intestinal continuity being maintained by an end-to-side gastrojejunostomy. At this time the vascular pedicle to the fundic pouch was completely severed; consequently this pouch was now totally denervated (fig. 5).

A month or so after the second operation, in each series of dogs, observations on acidity were made. These consisted in determinations of hydrogen-ion concentration with the quinhydrone electrode. In each instance various materials (beef extract, tenth-normal hydrochloric acid, gastric juice, etc.) were placed in the pyloric pouch and any effect on the acidity in the fundus or fundic pouch was noted. All observations were made following a fast of from eighteen to twenty-four hours. Animals of the first series were well trained so that the normal fasting reaction of the stomach was constant prior to making any experimental observations. At the conclusion of these studies the pyloric pouches were excised and examined histologically.

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10. Portis, B., and Portis, S. A.: Effects of Subtotal Gastrectomy on Gastric Secretion, *J. A. M. A.* **86**:836 (March 20) 1926.

11. Mann, F. C., and Bollman, J. L.: A Method for Making a Satisfactory Fistula at Any Level of the Gastro-Intestinal Tract, *Ann. Surg.* **93**:794 (March) 1931.

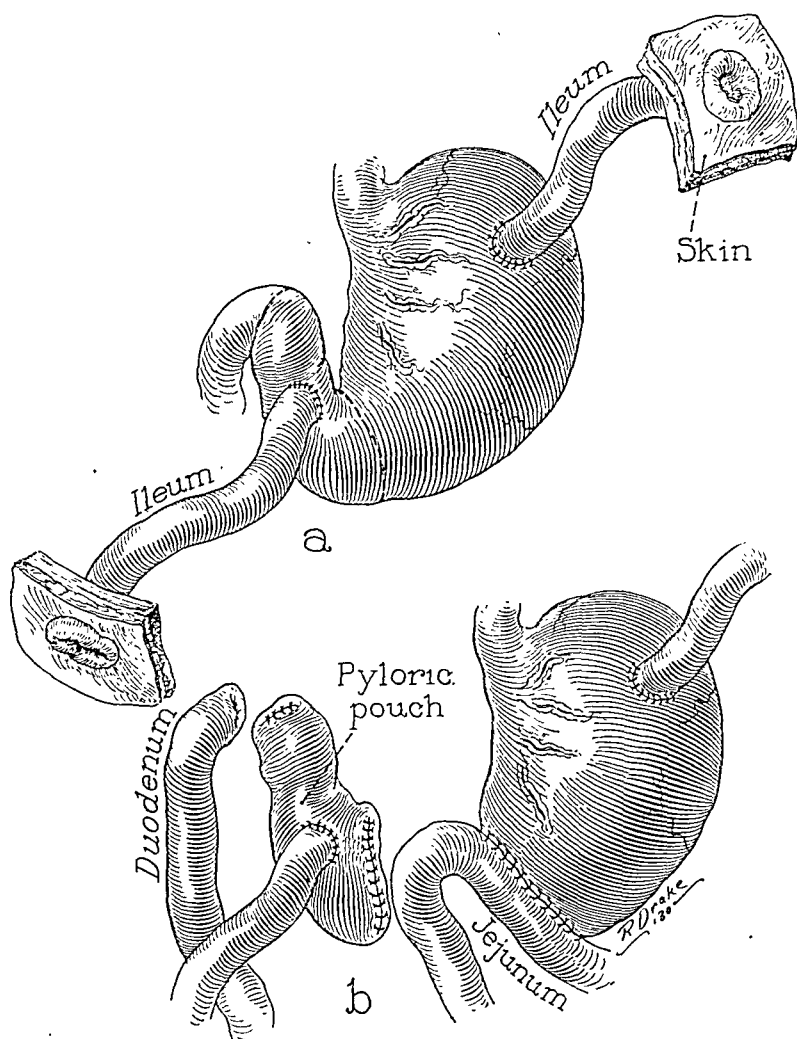


Fig. 4.—Isolated pyloric pouch and fistula in the fundus of the stomach.

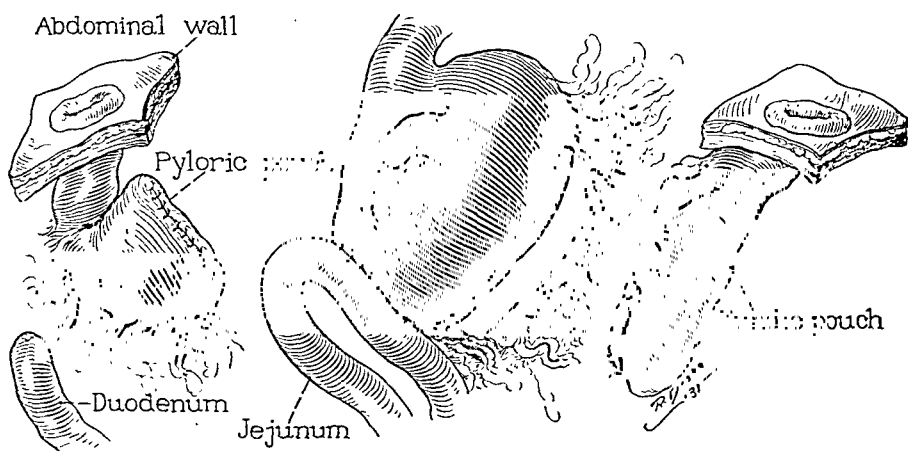


Fig. 5.—Isolated pyloric pouch and totally transplanted fundic pouch.

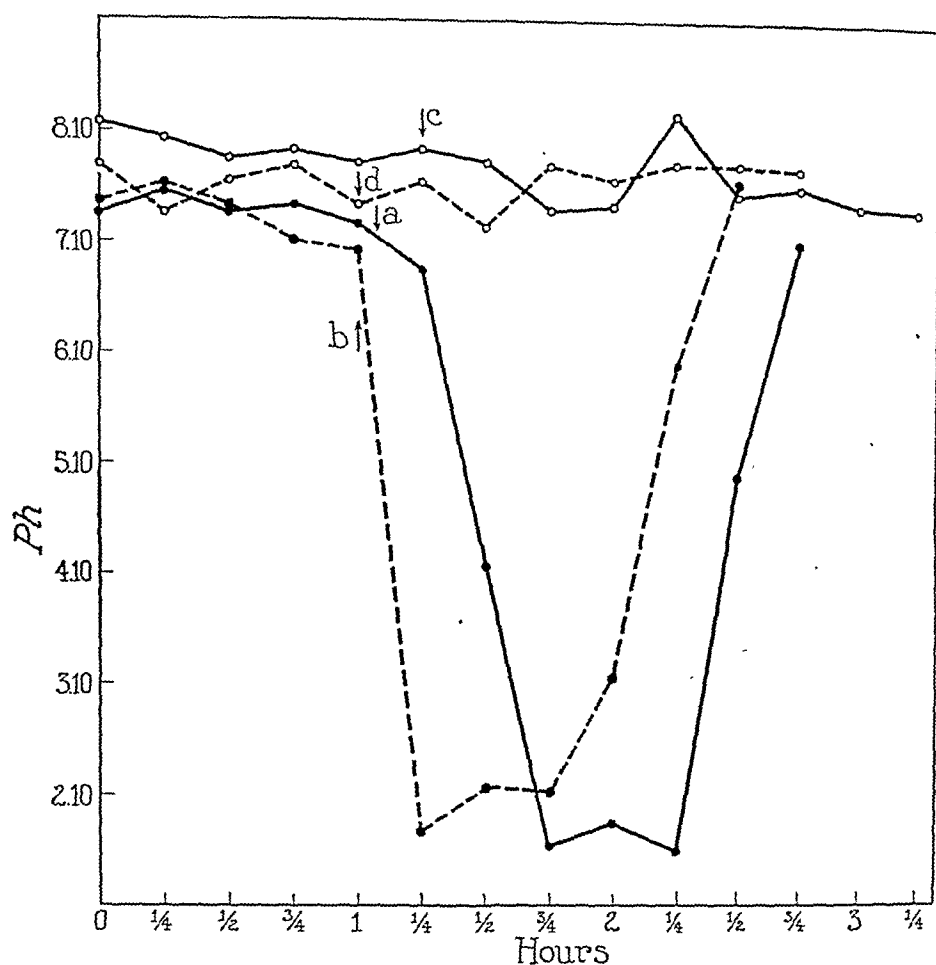


Fig. 6.—Four curves of hydrogen-ion values (expressed in  $p_H$ ) obtained on specimens removed from the fundus of the stomach: *a* shows results following the insertion of 5 cc. of beef extract into the isolated pyloric pouch; *c*, results following the insertion of gastric contents from another animal; *d*, results following the insertion of 5 cc. of tenth-normal hydrochloric acid, and *b*, a spurious positive result obtained when the animal was allowed only to smell the beef extract for thirty seconds. A similarity between *a* and *b* may be noted.

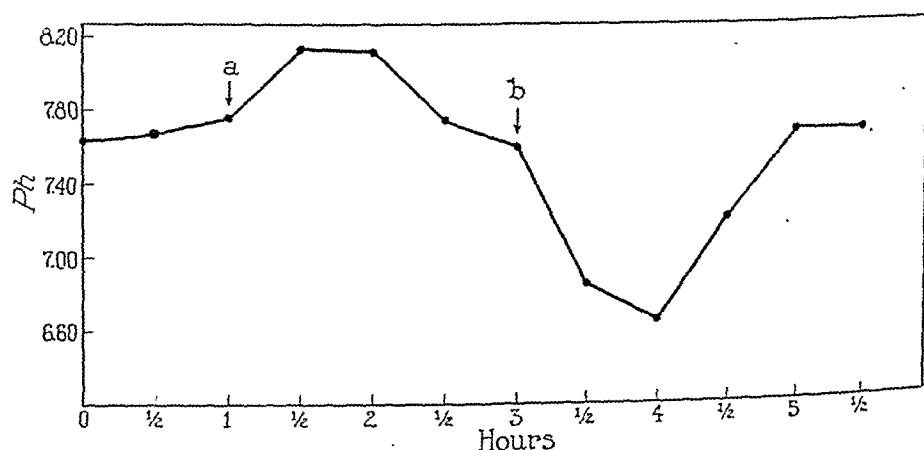


Fig. 7.—Curve of hydrogen-ion values (expressed in  $p_H$ ) in totally transplanted fundic pouch following *a*, the injection of 5 cc. of beef extract, dissolved in tenth-normal hydrochloric acid, into the pyloric pouch, and *b*, following subcutaneous injections of 1 mg. of histamine.

*Results.*—In the first series of dogs (pyloric pouch and fundic fistula) the early results were confusing. Sometimes beef extract, placed in the pyloric pouch, caused stimulation of fundic secretion and other times it did not. It was then observed that the positive results were apparently caused by secretion psychically initiated by smelling beef extract or, in some instances, actually licking some of this material from around the fistula to the pyloric pouch. Positive results of this type were not obtained with tenth-normal hydrochloric acid or gastric juice from another dog, which did not have a psychic appeal (fig. 6).

The dogs of the second series (pyloric pouch and totally transplanted fundic pouch) did not afford evidence of a humoral mechanism originating in the pyloric mucosa. Aqueous or acidified solutions of beef extract, gastric juice from another dog or tenth-normal hydrochloric acid, when inserted into the pyloric pouch, did not cause a significant change in the secretion of the fundic pouch (fig. 7). A test meal sometimes increased the secretion of the fundic pouch, which also suggests that the pyloric mucosa is not an essential feature of this mechanism.

*Comment.*—Care must be taken in the interpretation of negative results. In this work one might question the normal condition of the pyloric mucosa. Absorption appeared to be normal, although sometimes a trifle slow, as evidenced by the detection of iodine in the urine following the injection of sodium iodide into the pyloric pouch. Grossly the mucosa appeared normal, and microscopic sections did not reveal abnormality. Possible sources of error seemed more common with the positive than with the negative results. The former appeared to be invariably associated with psychic stimulation or leakage of the pyloric fistula.

In the intact animal, when the nerve supply to the stomach is undisturbed, it is not denied that the pyloric mucosa may be a minor factor in normal gastric secretion. However, this does not imply a true humoral mechanism.

#### CONCLUSIONS

The pyloric mucosa in the dog apparently plays only a minor part, if any, in gastric acidity.

Evidence was not obtained of a true humoral mechanism for gastric secretion initiated by absorption from the pyloric mucosa.



## A REVIEW OF UROLOGIC SURGERY

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*(Concluded from page 256)*

### BLADDER

*Tumor.*—Fey and Bompart<sup>24</sup> stated that total cystectomy is the only logical operative procedure for carcinoma of the bladder, and the late results have been satisfactory. Because of high mortality in the past it was almost abandoned, but it is now possible to reduce the immediate mortality by performing cutaneous ureterostomy before extirpation of the bladder. Beer reported 8 cases, in 7 of which cures lasted from two months to five years, with only 1 death. General condemnation of total cystectomy is not justified, but it is necessary to make use of a well regulated method in order to secure good results.

Papin first advocated exclusion of the bladder by means of bilateral iliac cutaneous ureterostomy as the safest way to prevent ascending infection, and as the best method by which to use artificial external devices for disposal of the urine. The prognosis depends entirely on the integrity of the ureters at the time of operation. If they are healthy and have preserved normal peristaltic movements, excellent results are possible.

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24. Fey, Bernard, and Bompart, Henri: *Technique de la cystectomie total pour cancer de la vessie*, J. d'urolog 32:165 (Aug.) 1931.

Fey and Bompert usually perform a two-stage operation, consisting first of cutaneous ureterostomy, followed six weeks or two months later by total cystectomy. In early cases it is possible to perform both procedures simultaneously, as is done by Beer. Cystectomy should be done by the extraperitoneal route if the summit of the bladder has not been invaded by the neoplasm. Precautions against infection are the careful disinfection of the bladder by lavage or instillations preceding operation, and the insertion of a Mikulicz drain in the cavity after removal of the bladder, to provide both drainage and hemostasis.

A transverse incision gives the best exposure. If the summit is in good condition, decortication is done, freeing first the anterior and lateral surfaces and then the summit and the posterior surface, care being taken not to open the peritoneum. If the neoplasm has invaded the summit, with marked pericystitis, removal of the peritoneal covering is not possible. The latter must be incised to the right and left, the bladder drawn upward and forward, after which the posterior surface is easily detached, down to the culdesac of Douglas; a wide peritoneal flap is isolated behind it, and the peritoneal gap closed by a catgut suture. If the peritoneum itself is invaded, it must be sectioned vertically on the right and left lateral borders of the bladder, down to the culdesac of Douglas, and the incision closed in T form. After this the removal of the bladder proper follows, consisting of freeing of the posterior and lateral surfaces, isolation of the pedicles, freeing of the anterior surface, exposure and section of the urethra, freeing of the inferior surface and section of the pedicle. The bladder, prostate gland and seminal vesicles are removed *en bloc* with the nearby cellular tissue.

Intestinal lavage is given on the third day after operation, the wound is dressed daily, the Mikulicz drain is removed gradually and hydrogen peroxide is used from the sixth to twelfth day, when the sac is removed. Four or five days later a Carrel tube is inserted, permitting irrigations with surgical solution of chlorinated soda.

Bompert<sup>25</sup> analyzed 111 cases of total cystectomy noted in the literature since the first case was reported by Bardenheuer in 1887. Death resulted in this case two weeks later. The first successful operation was that of Pawlick, in which the derivation of the urine was effected in the vagina; the patient survived for sixteen years. The high mortality that has heretofore accompanied the operation was due in a large degree to the various ingenious attempts to make a new bladder; these attempts included implantation of the ureters into the

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25. Bompert, H.: The Value and Indications of Total Cystectomy for Cancer, Arch. urol. clinique Necker 7:77 (Jan.) 1931.

rectum, sigmoid, cecum, vagina or urethra (leaving the ureters in the wound), nephrostomy and lumbar and iliac cutaneous ureterostomy.

The mortality from 57 implantations of the ureters into the intestine at various points was 45.6 per cent, the deaths being due chiefly to peritonitis, pyonephrosis and postoperative anuria. For physiologic reasons this is to be expected, since it is now established that every section and every suture of the ureter disturbs its motility, owing to the fact that it receives its motor innervation at its two extremities. When transmission of the motor influx is interrupted, atonia results, leading to dilatation of the upper part of the urinary tract and to atrophy or infection of the kidney. Infection is favored by intestinal contractions which cause backflow into the atonic ureter.

Suture of the ureters into the vagina produced poor functional results and painful dribbling. Leaving the ureters in the wound led to infection and to a 33 per cent mortality. The disadvantage of nephrostomy is that the fistula is in the back, where the patient has difficulty in caring for it.

Statistics indicate that better results are obtained when the operation is performed in two stages, the derivation of the urine being carried out at an earlier operation. In 81 cases in which total operation was performed in one stage, there were 40 immediate deaths, whereas in 26 cases in which operation was in two stages, the mortality was only 11.5 per cent.

The most satisfactory method of derivation of the urine appears to be by means of iliac ureterostomy, in which the ureters are anastomosed into the skin of the iliac region. This was first done by Le Dentu in 1889. It has been combined with total cystectomy in 21 cases, with only 6 (28.5 per cent) early deaths. It has the added advantage of permitting pyelo-ureteral catheterization and antiseptic lavage of the pelvis of the kidney.

The best time for operation is in the early stages of growth. The indication for total cystectomy, preferably by the two-stage operation, is present whenever there is an infiltrated tumor of the bladder, regardless of its situation.

[COMPILERS' NOTE.—The clinical results obtained in conservative treatment of carcinoma of the bladder by the use of radium implantation, deep roentgen rays, fulguration, open operation and partial resection of the neoplasm have been discouraging. When the tumor is of the infiltrating type more satisfactory results in early cases could be obtained by total cystectomy provided the operation is carried out in two stages and extraperitoneally, as Albarran long ago recommended. Papin also recently stressed the value of this radical procedure, advocating first transplantation of the ureters to the skin and at a later

time total cystectomy *en bloc* or leaving the prostate gland and seminal vesicles if these tissues are not involved. The problem of transplanting the ureters to the bowel has been considered in American literature principally by Coffey and by W. J. Mayo and C. H. Mayo. The improved technic of the Coffey method, making use of two large catheters attached to the end of the ureters and leading them through the lumen of the rectum, provides better drainage and to a certain extent prevents ascending infection. This method has also been recently used by Kirwin in an experiment on dogs, but as yet his conclusions appear to be far from satisfactory.]

Begg<sup>26</sup> stated that adenoma or adenocarcinoma is probably the most common tumor of the apex of the bladder. Besides describing his own case, he reviewed 17 cases from the literature.

The tumors of the urachus at the apex of the bladder, although frequently not recognized as such, are the most significant clinical group. On the assumption that the urachus normally extends as far as the navel, any lesion occurring in the upper part of the space of Retzius has erroneously been attributed to the urachus. In many cases tumors and other abnormal conditions in this region have no connection with the urachus.

Begg concluded that primitive cells of the urachus are always present in the muscular wall at the apex of the bladder. These have a tendency to form tumors of the intestinal type. Adenomatous and cystic formations of various kinds are commonly found in connection with the lower end of the urachus, and the connection between these and the colloid carcinomas can be followed through all the stages. When instituting treatment all tumors of the apex of the bladder must be assumed to be of urachal origin, unless the contrary is proved. The treatment is radical operation, removing the umbilicus and all the tissues between it and the bladder, as well as a large portion of the latter.

[COMPILERS' NOTE.—Colloid adenocarcinomas form a distinctive group of tumors involving the bladder. Adenocarcinomas of the bladder are closely allied to adenomas and develop similarly. These tumors, differing from all other vesical growths, have a predilection for the upper part of the bladder, particularly the dome, which suggests an origin from remnants of embryonal inclusions.

De Korte has described a glandular carcinoma removed from the apex of the bladder of a woman, aged 50. The growth did not recur, but the patient died shortly after the operation. Adami, who examined

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26. Begg, R. C.: The Colloid Adenocarcinomata of the Bladder Vault Arising from the Epithelium of the Urachal Canal: with a Critical Survey of the Tumours of the Urachus, *Brit. J. Surg.* **18**:422 (Jan.) 1931.

this tumor, concluded that it originated from urachal remains in the wall of the bladder. Barringer reported an unusual adenocarcinoma involving only the apex of the bladder; the larger part was above the bladder. Ewing, who examined the tumor, said that the growth was unique and that possibly it came from a remnant of the allantoic end of the bladder or developed from a cloacal inclusion.]

Pfahler<sup>27</sup> stated that pneumocystography is a valuable means of determining the presence, size, outline, position and amount of infiltration of carcinoma of the bladder. It may be done with a sterile catheter, atomizer bulb and a hemostatic forceps by any roentgenologist using reasonable care. Roentgenotherapy consists of the use of radium in the form of capsules, needles or seeds and of deep roentgen ray treatment alone, or before or after electrocoagulation. Better results were apparently obtained with electrocoagulation than with excision followed by radium or roentgen ray treatment. Irradiation alone usually relieves hemorrhage and pain.

Dean and Quimby,<sup>28</sup> in reporting on irradiation of carcinoma of the bladder, stated that if the base of a papillary carcinoma is not more than 1.5 cm. in diameter and is entirely visible through the cystoscope, the tumor may be treated successfully with gold radon seeds implanted through the urethra. Larger papillary carcinomas and all infiltrating tumors should be treated under full vision with the bladder opened. Relatively large doses of interstitial irradiation are used by the authors because malignant tumors in an organ as inaccessible as the bladder should be cured by a single treatment. Their results with the use of adequate doses of interstitial irradiation for carcinoma of the bladder indicate that there is a possibility of cure in cases in which operation alone, short of total cystectomy, can offer nothing. Their operative mortality was 3.7 per cent as compared with from 10 to 20 per cent from operation alone. In from 43 to 55 per cent of a series of cases of papillary carcinomas of the bladder, and in from 27.8 to 31.8 per cent of a series of cases of infiltrating carcinomas of the bladder, the patients are free from symptoms and signs of disease three years after treatment.

[COMPILERS' NOTE.—Reports on the results of treatment of tumors of the bladder are difficult to evaluate because of lack of uniformity in pathologic classification. In America the trend of opinion is to consider all growths of the bladder, even simple papillomas, as potentially malignant. Broders' grading of epithelial neoplasms is being more

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27. Pfahler, G. E.: *The Roentgen-Rays and Radium in the Diagnosis and Treatment of Carcinoma of the Bladder*, Surg., Gynec. & Obst. **53**:680 (Nov.) 1931.

28. Dean, A. L., Jr., and Quimby, Edith H.: *Radiation Therapy of Carcinoma of the Bladder*, Surg., Gynec. & Obst. **53**:89 (July) 1931.

generally applied to this type of lesion and may serve to give a better basis for classification within a few years. McDonald follows the classic procedure of wide resection in extensive and doubtful tumors. Advocates of the use of radium and diathermy, such as Dean and Quimby, offer much evidence of the advantages to be gained from these forms of treatment. In the individual case, excluding the small simple papillomas from consideration, treatment at present will vary with the judgment and experience of the individual surgeon.]

*Cystostomy.*—Vermooten<sup>29</sup> stated that at the New Haven Hospital preliminary suprapubic cystostomy is performed only if drainage by catheter is unsatisfactory, if a catheter cannot be tolerated or if severe urethritis or epididymitis develops. It is also performed for some operative procedure on the bladder itself or for permanent vesical drainage. Hence these statistics cannot be compared with those from cases in which suprapubic drainage is done preliminary to suprapubic or perineal prostatectomy. Keyes stated that without prevesical section the mortality from suprapubic cystostomy between 1917 and 1922 at Bellevue Hospital was about 33 per cent, whereas at a private hospital the mortality was 14 per cent. Pelvic cellulitis was the predominant cause of death.

During the last four years suprapubic cystostomy was performed in 77 cases in the New Haven Hospital. Twenty-three of the patients (30 per cent) died: 18 following cystostomy alone, 2 after suprapubic cystostomy and diverticulectomy, 1 following the insertion of radium and 2 subsequent to removal of the prostate gland. In 11 cases the wounds were apparently not infected and did not leak urine. Data were not available in 16 cases. In 50 cases (65 per cent) there was definite suppuration of the wound with or without urinary drainage around the catheter, through the wound or both.

Vermooten uses a cystotome designed by Kidd of London. Under local or general anesthesia, the bladder is exposed through a low median line suprapubic incision; the incision is long enough to obtain a satisfactory exposure of the distended bladder. The peritoneal reflection is pushed up, exposing the entire anterior surface of the fundus of the bladder. The distended bladder is gripped and firmly held with clamps of mucosa, and a two-wing malecot catheter is inserted with the use of the Kidd perforator and introducer. The cystotome is removed and the vesical contents are allowed to drain into a receptacle. As the bladder empties, it contracts. When empty, it hugs the tube so closely that urine cannot escape. The wound is irrigated with a solution of sodium

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29. Vermooten, Vincent: The Prevention of Perivesical Cellulitis and Suppuration Following Suprapubic Cystostomy by the Use of Kidd's Perforator and Introducer, *New England J. Med.* 205:473 (Sept. 3) 1931.

chloride and closed. A rubber sheath drain is placed in the space of Retzius and removed from twenty-four to forty-eight hours later. Two stay sutures hold the wound together. The rectus fascia is approximated with interrupted sutures of chromic catgut. The tube is tied in with a heavy silk suture passed through the skin.

*Trigonal Obstruction.*—Campbell<sup>30</sup> coined the term "trigonal curtain" to designate an obstructive lesion of the vesical outlet which he found in an infant and treated by transvesical excision. The condition is a congenital malformation and is not to be confused with so-called floating trigone.

The trigonal curtain, which was really a large mucosal redundancy, 3 mm. thick, originated in the lateral trigone and wall of the bladder on each side and thence passed forward about midway between the vesical outlet and interureteric ridge. The ureteral orifices were behind the obstruction. Below, the curtain was integral with the trigone; there were no attachments to the anterior wall of the bladder above. In the median line the obstruction was 2 cm. high and so thoroughly covered the vesical outlet that at operation the mushroom head of a moderate-sized indwelling Pezzer catheter was completely hidden beneath the curtain. Whenever the patient attempted to urinate, the curtain flapped forward and almost completely blocked the vesical outlet. Urinary difficulty, retention, infection, marked dilatation of the entire upper part of the urinary tract and backpressure renal injury resulted. Decompression of the bladder with free drainage was carried out for many days preoperatively, and undoubtedly contributed somewhat to the ultimate surgical success.

At operation, through the open bladder, the obstructing curtain was resected by clamp and suture. The floor of the bladder was sewed with a double layer of fine chromic gut. Recovery was uneventful, except for marked distention during the first seventy-two hours. The wound healed completely in three weeks. Periodic examinations have shown marked diminution of infection. Six months after operation, the child voided freely and emptied the bladder completely.

Frontz and Landes<sup>31</sup> stated that trigonal hypertrophy should be regarded as a compensatory reaction to the development of pathologic conditions involving the vesical orifice which interfere with the opening of the internal sphincter. An obstruction such as fibrous contracture of the vesical orifice, carcinomatous involvement of the median portion of the internal sphincter and hypertrophy of the median lobe are the

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30. Campbell, M. F.: Trigonal Curtain Obstruction of the Bladder Outlet, *J. Urol.* **27**:157 (Feb.) 1932.

31. Frontz, W. A., and Landes, H. E.: The Clinical Significance of Trigonal Hypertrophy, *J. Urol.* **27**:145 (Feb.) 1932.

common lesions producing trigonal hypertrophy. The absence of trigonal hypertrophy excludes the presence of these conditions. Obstructions due to hypertrophy of the bilateral lobe, congenital valvular obstructions of the posterior urethra and urethral stricture produce hypertrophy of the detrusor muscle without hypertrophy of the trigone.

*Bilharziasis.*—Culver and Hoepfner<sup>32</sup> stated that vesical bilharziasis, or infestation with *Schistosoma haematobium*, is a relatively rare disease in this country. Twenty-five cases have been reported in the literature. Bilharziasis includes a group of diseases resulting from invasion of certain species of unisexual flatworms of the family Schistosomidae, and results from irritation and inflammatory reactions due to the toxins produced by the worms. The diseases are produced chiefly by the presence of the ova in the walls of the bowel, the urinary tract and the liver. The worms live in the portal system and migrate to the finer mesenteric veins to deposit their eggs within the wall of the bowel. The species *Schistosoma haematobium* migrate through the hemorrhoidal veins to the wall of the bladder. In the urinary tract the earliest localizing symptom is burning on urination, associated with frequency; later there is characteristic terminal hematuria, often accompanied by suprapubic distress, especially with a distended bladder.

Local lesions of the urinary tract are definite and variable, and occur in the following order: (1) Deposits of mature worms and their ova in the region of the base of the bladder produce patches of hyperemia and small extravasations of blood; (2) further chronic irritation and tissue reaction result in papillary granulations, which most commonly are around the ureteral orifices; (3) definite sandy patches may be seen, due to calcified ova within the mucosa; (4) vesical calculi frequently result from detached portions of papillary structures acting as nuclei; (5) later the wall of the bladder may become infiltrated deeper, resulting in thickening and fibrosis; (6) the obstructive situation of the papillary granulations about the ureteral orifices eventually results in hydronephrosis and hydro-ureter with the usual tendency of these obstructive conditions to become septic, and (7) carcinoma of the bladder from irritation results.

Culver and Hoepfner reported a case of bilharziasis of the bladder successfully treated by intravenous injections of antimony and potassium tartrate which completely removed all clinical evidence of activity of *Schistosoma haematobium*, which had been present for more than a year. The authors also removed the obstructing papillary granulations of the ureter by fulguration, and subsequent dilatation of the ureters resulted in a return of the renal function to normal.

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32. Culver, Harry, and Hoepfner, W. F.: Vesical Bilharziasis, J. Urol. 27: 189 (Feb.) 1932.



## PROSTATE GLAND

*Hypertrophy.*—Suter<sup>33</sup> analyzed 300 cases of prostatectomy in which he did not operate until it was imperative. Janssen, on the other hand, performs operation early in order to eliminate the possibility of carcinoma and to obtain better operative results.

The following statistics illustrate the incidence of carcinoma of the prostate gland: Albarran and Hallé reported an incidence of 14 per cent in cases of hypertrophy of the prostate gland. Many observers have found from 5 to 25 per cent in adenomas. Green and Brooks found 5 per cent; Zuckerkandl, 10 per cent; Young, 20 per cent, and Moullin, 25 per cent. In 1922 Geraghty found, in a series of 450 cases of carcinoma of the prostate gland, that hypertrophy was associated in 75 per cent. In every case it originated not from the adenoma, but from the surgical capsule. This was substantiated by Suter's observations.

Only simple tests of renal function were used. If the specific gravity was less than 1.018, Volhard's concentration method was employed, and if it was doubtful, the sodium indigotindisulphonate method was used. In many cases the chemical constituents of the blood also were determined. For poor operative risks drainage was instituted for long periods, either by catheter or by cystotomy. Parasacral anesthesia is preferable, and air inflation was used to open the bladder. Hemorrhage was controlled chiefly with gauze packs dipped in epinephrine or with tampons. Gelatin and calcium preparations were also used. Postoperative treatment consisted chiefly of lavage of the bladder with physiologic solution of sodium chloride and the use of the indwelling urethral catheter until the fistula healed. It is Suter's belief that the presence of infection affords a better prognosis. His mortality was 4.3 per cent.

Kretschmer<sup>34</sup> stated that occasionally a case is cited in which recurrence has followed apparently complete removal of the prostate gland. Two cases are reported in which he performed suprapubic prostatectomy for benign hypertrophy and operated for recurrence. The periods between the two operations were ten and twelve years, respectively. Similar long periods between operations have been reported: nine years by Blum, ten years by Casariego, twelve years by Frohstein and Meschebowski, sixteen and fourteen years by Gregora, six years by Takahashi, ten years by Thomson-Walker and six years by Zuckerkandl.

Recurrence of benign hypertrophy of the prostate gland can be explained in one of two ways: If it is so difficult to remove the prostate

33. Suter, F.: Bericht über 300 Suprapubische Prostatektomien, *Ztschr. f. Urol.* **25**:241, 1931.

34. Kretschmer, H. L.: Recurrence Following Suprapubic Prostatectomy for Benign Hypertrophy, *Surg., Gynec. & Obst.* **53**:829 (Dec.) 1931.

gland that it must be removed in pieces or by morcellement, a small nodule may be left behind; later the nodule becomes enlarged and causes obstruction. A second possibility is that the recurrences may originate from small tubules in the layers of the capsule remaining in the prostatic bed. Because of their microscopic size, they are not recognized at operation.

In Gregora's review of the literature he noted 30 cases of recurrence of benign hypertrophy of the prostate gland, a small number considering the frequency with which prostatectomy is performed.

Lowsley and Kirwin<sup>35</sup> summarized 50 cases of suprapubic prostatectomy taken from their records, but did not present conclusions as to the advantage of this procedure over others. Forty-four patients had benign hypertrophy of the prostate gland, 5 had carcinoma and 1 had a granuloma. The shortest period of hospitalization was twenty-six days, the longest one hundred and thirty-two days and the average about six weeks. Only 1 patient died from the immediate effects of operation; this was the oldest of the series, and death was caused by postoperative shock. The total mortality for the series was 8 per cent.

Peacock<sup>36</sup> stated that in order to close the urinary bladder primarily there should be complete hemostasis and unobstructive urethral drainage. In his method of performing this procedure after prostatectomy, the edges of the capsule are caught with a tenaculum after enucleation of the prostate gland. The prostatic bed and capsule are then sutured, reconstructing the internal urethral orifice. The bladder is closed with a double row of Lembert sutures. Drainage is not used.

In almost all of 50 cases the operation was done in two stages from seven days to five months apart; the average interval was two weeks. Wounds healed as well after the second stage of the operation as they did at the first. Normal voiding was established within an average of twelve days.

Sargent,<sup>37</sup> in reporting on suture of the prostatic capsule after prostatectomy and primary closure of the bladder, stated that the techniques, described by Lower and by Harris, of stitching the prostatic bed differ from each other and from his method. It has not been possible for Sargent to visualize the depth of the bleeding prostatic bed sufficiently to permit the dot and dash stitching described by Lower, or to reconstruct surgically the prostatic urethra as so elaborately set forth by Harris. In a consecutive series of 37 cases of prostatectomy, in 5 of

35. Lowsley, O. S., and Kirwin, T. J.: Suprapubic Prostatectomy, *J. A. M. A.* **97**:1669 (Dec. 5) 1931.

36. Peacock, A. H.: Suprapubic Prostatectomy with Closure of Bladder, *J. A. M. A.* **97**:1768 (Dec. 12) 1931.

37. Sargent, J. C.: Suture of the Prostatic Capsule After Prostatectomy and Primary Closure of the Bladder, *J. Urol.* **26**:639 (Nov.) 1931.

which the procedure was in two stages, complete hemostasis was easily obtained and the cavity of the prostatic bed was obliterated by drawing the posterior edge of the torn capsule into the depths of the bed with one or two boomerang sutures and then closing the internal orifice snugly around an indwelling urethral catheter by three or four transverse anterior stitches. The bladder was then closed with a double layer running suture and the abdominal wound drained only by a wick in the space of Retzius. Cystoscopy from six to twenty-one days after operation has shown that the stitching does not effect primary healing of the prostatic margin, but accomplishes perfect hemostasis and the collapse of the prostatic bed.

In accordance with the findings of Lower and later of Harris, Sargent observed that, with the prostatic bed obliterated, hemorrhage controlled and the bladder closed tightly, drainage by urethral catheter is ample for all purposes; that even though many wounds seep urine a few days after removal of the catheter, they close promptly and are free from slough; that the immediate postoperative comeback is in sharp contrast to the Freyer operation, and that the ultimate period of recovery of these patients is shortened by weeks.

*Anesthesia.*—Davis<sup>38</sup> reported the use of sacral block anesthesia in 378 cases of perineal prostatectomy. In each case a caudal injection was given into the first, second and third posterior sacral foramina. The percentage of failure of anesthesia was high<sup>20</sup> in the first 25 cases, but decreased gradually during the first 100 cases until it ceased. The number of failures in the first 100 cases was 12, 9 of which occurred in the first 50. Since the first 100 cases there has been only 1 failure; successful anesthesia has been obtained in the remaining 229 consecutive cases of the series.

There were 9 deaths (2.38 per cent) in 378 consecutive cases of perineal prostatectomy in which sacral anesthesia was used. The largest number of consecutive cases included in this series without any mortality was 121. None of the deaths was in any way associated with the anesthesia.

The following are significant factors in minimizing the mortality rate in prostatectomy: 1. Adequate and prolonged preliminary drainage. A minimal ten day drainage period was required in all cases, regardless of the apparent good general condition of the patient; in many cases it was extended over several weeks and, occasionally, over several months. A ten day period of normal temperature also preceded every operation. The suprapubic drainage route was used in about 25

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38. Davis, Edwin: Sacral Block Anesthesia in Perineal Prostatectomy: Its Infallibility When Accurately Administered, J. A. M. A. **97**:1771 (Dec. 12) 1931.

per cent of cases in which the retained urethral catheter was intolerable or inefficient. 2. Comparative figures showing that the perineal route has a lower hazard than the suprapubic. 3. Excessive care in hemostasis. Immediate postoperative hemorrhage, in every case, is controlled by means of a combination hemostatic and drainage bag. 4. Sacral block anesthesia. There have been no deaths or alarming reactions in the series from its use.

[COMPILERS' NOTE.—Davis' well controlled statistics indicate what excellent results may be obtained by an experienced, careful operator. The urologic surgeon, more often than any other, deals with cases in which renal function is diminished. Anesthesia that will not appreciably increase the work of the kidneys, such as sacral anesthesia, is desirable. Many patients presenting themselves for relief of prostatic hypertrophy or disease of the bladder are usually well along in years, and frequently have also associated urinary obstruction and renal insufficiency. Renal infection and chronic nephritis are common, and are responsible for the majority of deaths following prostatectomy and resection of the bladder. The anesthesia employed is closely associated with the incidence of undesirable postoperative sequelae in cases of urinary obstruction. Ether unquestionably predisposes to complications of the pulmonary and cardiorenal types, and the incidence of postoperative bleeding, which greatly increases the liability to urinary infection, is comparatively high following spinal anesthesia. Unquestionably, sacral anesthesia is safer than either ether or spinal anesthesia.

In a reported series of 526 cases of prostatectomy, sacral anesthesia was employed in 270 with a mortality of 3.33 per cent. In contrast to this, spinal anesthesia was employed in 187 cases; the mortality was 6.95 per cent. In 69 cases ether was used, following which 7.24 per cent of the patients died.]

Crockett and Washburn<sup>39</sup> reported on the analysis of the first 100 answers to a questionnaire sent to patients operated on for hypertrophy of the prostate gland in the last eight years. Five of the questions concerned urinary function and conditions since operation; 5 considered the health otherwise, and 4 pertained to the mental reaction to the operation.

Ninety-three per cent of the patients reported better health; 1 per cent unchanged health, and 6 per cent that health was not so good since leaving the hospital. Thirty-six per cent had no nocturia; 19 per cent urinated only once at night; 15 per cent, twice or less; 11 per cent, 3 times or less, and 11 per cent, 4 times or less. Eight per cent reported

39. Crockett, F. S., and Washburn, W. W.: Progress of the Prostatic After He Has Left the Hospital. *J. Urol.* 26:643 (Nov.) 1931.

nocturia of 5 or more times. Ninety-one per cent had no difficulty in starting urination, and 9 per cent had some trouble. Ninety-six per cent had never noticed blood in the urine; 4 per cent reported hematuria. Three per cent did not reply to the question concerning dribbling; 72 per cent were free from this condition; 19 per cent had dribbling only after voiding, which may have been due to technic rather than to function. Six per cent had dribbling at all times.

Eighty-eight per cent of patients were well or better than before operation; 12 per cent were not so well. Ninety-five per cent were satisfied with the results; 5 per cent were not satisfied or qualified their answers. Ninety-nine per cent considered the operation worth while, and 1 per cent did not. Ninety-five per cent stated, with varying degrees of enthusiasm, that they would advise others to have the operation; 1 per cent did not reply, and 4 per cent did not answer in the affirmative.

Nesbit,<sup>40</sup> two and a half years ago, working with Cabot, found that of 450 patients operated on for obstruction of the prostate gland with drainage, 17 per cent had epididymitis. Since then they had performed vasectomy in all operations on the prostate gland as a pre-operative measure. In more than 100 cases there has been an incidence of less than 1 per cent of epididymitis. In the case that did occur there were chills and fever following operation and immediately preceding the epididymitis, and it was thought that probably the infection was blood borne.

*Resection.*—McCarthy<sup>41</sup> has employed his visualized electrotome in cases ranging from simple fibrosis of the prostate gland to complete retention from hypertrophy of the middle and lateral lobes, and in cases of malignant disease of the prostate gland, with satisfactory immediate results. It has not been employed and perhaps should not be employed for the large intravesical or the vascular type of gland or in cases of so-called prefibrosis, a subacute inflammatory process.

The operation is essentially a hospital procedure, and the patient should receive the same study and preparation, with the same precautionary measures as are taken in any well regulated institution.

Procedures for excision of the prostate gland are begun at the floor of the sphincter of the median line, with the cutting loop well extended into the visual field and behind the obstruction, the sheath of the instrument as far forward in the region of the verumontanum as is consistent with visualization and safety. The cutting loop is then brought into contact with the vesical aspect of the obstruction. The current is begun and the loop brought forward with a slow, steady

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40. Discussion on Prostatectomy, J. A. M. A. **97**:1775 (Dec. 12) 1931.

41. McCarthy, J. F.: Suggestions as to Procedure in the Use of the McCarthy Visualized Prostatic Electrotome, J. Urol. **27**:265 (Feb.) 1932.

movement until it is completely within the sheath. Slow movement seems to minimize bleeding. Immediately after each cutting the electrotome is removed from the sheath, and if it does not bring with it the sectioned piece, the latter may come with the irrigating fluid. Generally two or more grooves are taken on the floor of the sphincter. After completion of the floor of the sphincter, first one lateral lobe and then the other is treated in a manner similar to the floor. On completion of the operation, a French whistle tip soft rubber catheter is passed through the sheath into the bladder. After resection strict aseptic irrigation is done every half hour or at longer intervals according to the needs of the case and to obviate blocking. Any interruption in drainage should be immediately corrected. Urinary antiseptics are applied.

McCarthy gives a final admonition against excessive enthusiasm. The method deserves discerning investigation and judicious evaluation. It will not be fostered by impulsive decision or hindered by prejudicial neglect.

Crowell and Davis<sup>42</sup> presented their method of resection on the prostate gland. They employ an instrument that has numerous improvements on the one originally devised by Stern and that permits the correction of practically all types of obstruction of the vesical orifice. The instruments are the generators for producing a suitable cutting and coagulating current, an arrangement that permits instantaneous interchange of these currents, and the instrument of application.

Resection of the prostate gland is performed under sacral or caudal anesthesia. The resectoscope sheath is introduced, the obturator removed and the bladder irrigated with sterile water until the return is clear. Visual inspection of the vesical orifice and posterior urethra is made by means of the observation telescope. It is important to determine accurately the site and amount of obstructive tissue. The verumontanum, which is always at the apex of the gland, is used as the anterior guide and should be located before removal of the tissue is begun. The site of the initial section, usually at the vesical aspect of the orifice, is made to engage within the fenestrum. The loop rests on the tissue protruding through the fenestrum. With the cutting current turned on, the loop is slowly advanced the entire length of the fenestrum, removing a section of tissue of about 1 to 2.5 cm. and leaving a clean gutter. At the time of each section, with continuous irrigation, it should be determined if there is any hemorrhage. If it occurs, the other foot switch is used, the loop is slowly returned through the gutter and the current coagulates the bleeding vessel, com-

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42. Crowell, A. J., and Davis, T. M.: Motion Picture Demonstration of Prostate Resection, *J. Urol.* **26**:629 (Nov.) 1931.

pletely arresting the hemorrhage. In the bar of contracted vesical neck, sufficient parallel sections are made in the floor of the sphincter completely to remove the obstruction. In lateral lobes that encroach on the posterior urethra, sections are made in a continuous line, having the proximal edge of the preceding section in view at the distal edge of the fenestrum.

A total of 230 resections of the prostate gland has been done by Crowell and Davis by this technic at the time of this report, classified as follows: contracted vesical orifice, 18 cases; median lobe, 60; unilateral lobe, 8; unilateral and median lobe, 29; bilateral lobes, 41; bilateral and median lobes, 31; carcinoma, 30; following perineal prostatectomy, 2, and after suprapubic prostatectomy, 11.

There have been exceptionally few complications and no deaths following these resections. In a case in which there were large bilateral and middle lobes the cardiac condition was serious. The excessive hemorrhage caused by passing the examining cystoscope was controlled by the resectoscope equipment; and the patient left the hospital three days postoperatively. Death, which occurred three weeks later, was due to heart trouble. In 7 of the earlier cases, a second operation was required, sufficient tissue not being removed during the initial operation. In the other cases the obstruction was removed by the first operation.

In most cases the bladder empties completely following operation. At a check-up examination the residual urine had been reduced to less than 30 cc. in every case. Most of the patients were free from infection in the urine two months after operation. One hundred and six patients urinate only once at night; 38 urinate occasionally at night; 12 two to three times at night, but normally during the day. The remainder report that they are free from urinary symptoms. The average stay in the hospital was four days; 3 patients remained two weeks and 14 remained one week.

Davis<sup>43</sup> stated that intravesical and intra-urethral enlargement of the prostate gland causes the obstructive type of prostatism. From his experience in more than 200 resections it is not necessary to remove the entire gland, but only that portion producing the obstruction, in order to relieve the patient's symptoms. With the resectoscope, it is possible to remove the entire gland completely under direct vision and rectal palpation, with the sheath of the instrument *in situ*. Excellent results have been obtained by removing only the obstructing tissue.

The preparation for resection is that generally employed in obstructive conditions. In cases of extremely large bilateral lobes, the length

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43. Davis, T. M.: Prostate Operation: Prospects of the Patient with Prostatic Disease in Prostatectomy vs. Resection, J. A. M. A. 97:1674 (Dec. 5) 1931.

of anesthesia may not permit the removal of the two lobes at a single operation. A two-stage resection, removal of one lobe at the first sitting and the other several days later, is then performed.

In bars and contractures, for accuracy and ease of operation, resection is particularly suitable and more radical measures are not necessary. Resection is also recommended in cases of extensive hypertrophy and inoperable carcinoma, rather than major surgical procedures or permanent suprapubic drainage, because of the freedom from mortality and discomfort to the patient.

Randall<sup>40</sup> is of the belief that no instrument now in use or yet to be devised will ever enable complete prostatic adenectomy as is accomplished by open operation. Partial removal of the prostate gland may give clinical results which to all appearances may be designated as a cure. In Randall's opinion the stability and the possibility that partial removal and temporary results of Davis' methods, with the likelihood of gradually recurring obstructions, will give a sense of false security. Although Davis' method is a stimulating advance in technic, it is a highly technical procedure; it cannot remove all the hypertrophied gland, and probably in the hands of most surgeons it will meet with failure.

Crowell<sup>40</sup> stated that transurethral resection of the prostate gland has a definite field in operations on the prostate gland. The procedure is applicable in at least 90 per cent of the cases. Since Jan. 1, 1931, Crowell and his associates have performed prostatectomy only 4 times in 62 cases.

Lowsley<sup>40</sup> is of the belief that Davis' instrument and method should not be used by every surgeon or in every case. By this method one cannot remove the whole prostate gland. There will be a group of recurrences which will cause the procedure to be abandoned in certain cases. Kirwin, Collings and Stern take the more conservative view that this type of prostate gland should not be operated on in the manner described by Davis. Lowsley stated that he had attempted to show that the intra-urethral method of removing the gland should be avoided because of the danger of tearing into the plexus of Santorini.

Bumpus<sup>40</sup> stated that, after witnessing Davis perform 4 resections of the prostate gland and seeing other patients who had been operated on previously, he felt that the results and the ease of the procedure have in no way been exaggerated. The modern punch operation as practiced by Davis, by removing all obstruction, completely relieves the patient of residual urine and is likewise successful. If obstruction is relieved, the indications for removing the whole gland disappear. An elderly patient who would not consent to the loss of the gland by a major operation would usually allow symptoms of obstruction to be relieved by this simple procedure.



Morrissey<sup>40</sup> stated that the immediate results obtained by Davis are an improvement on those which he had obtained in the past. The limitations to Davis' method are that the loops are weak, and the electric knowledge and patience required for manipulation of the instrument are not possessed by the average genito-urinary surgeon.

*Carcinoma.*—Nelson<sup>44</sup> stated that since any treatment for an obstructing carcinomatous prostate gland is only palliative, all that can be accomplished by coagulation is vesical drainage and not cure. He uses the following technic, with sacral or spinal anesthesia: After removing tissue for microscopic section, the coagulation is done through a cysto-urethroscope by means of a large electrode. The bipolar current from a high frequency machine is used. All nodules and tissue that project into the prostatic urethra and vesical neck are thoroughly coagulated. The coagulated tissue is then removed by means of a visualized punch. If there is a large flat surface so that the Young or the Braasch punch cannot grasp any tissue, the Kirwin punch is used. As soon as the punching causes bleeding, so that the field is obscured, the cysto-urethroscope is reintroduced and coagulation resumed. Coagulating and punching are alternately carried on until the prostatic urethra and vesical neck are formed into a wide open tunnel. After the operation is completed, continuous drainage is maintained for three or four days by a catheter retained in the urethra, following which normal urination may usually be resumed.

The method was used in 16 cases: in 7 cases of carcinoma of the prostatic capsule following prostatectomy for benign hyperplasia; in 3 cases of carcinoma and obstructing benign adenoma, and in 6 cases of carcinoma of the prostate gland with little if any benign hyperplasia. In all the cases of the first group the coagulation treatment gave good results in relieving the urinary symptoms and reducing the amount of residual urine. Six of these 7 patients are living; 4 of them have each had 2 treatments. The length of time that a single treatment has maintained vesical drainage has been from four to ten months. The series of 3 patients was treated by suprapubic operation to remove the benign adenoma, and the coagulation was done cystoscopically several months later after the carcinoma had caused obstruction. The results in these instances were fairly satisfactory although duration of life was rather short. Four of the 6 patients in the last group, who had neoplasms of a low degree of malignancy, obtained good results.

There were no deaths that could be attributed to cystoscopic coagulation, nor was shock observed following the procedure. In 2 cases

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44. Nelson, O. A.: *Electro-Coagulation in Carcinoma of the Prostate*, J. Urol. 26:681 (Nov.) 1931.

in which the growth had extended to the external sphincter, incontinence followed coagulation, and was troublesome for five or six weeks. It has not been necessary to resort to cystotomy to relieve the obstruction in the cases in which cystoscopic coagulation for a carcinomatus obstructing prostate gland had been used, although it had been necessary to repeat the procedure. The longest period that any patient had been free from obstruction after coagulation was eighteen months, and the shortest, six weeks.

O'Crowley, Trubek and Goldstein<sup>45</sup> presented 2 cases of carcinoma of the prostate gland and extensive osteosclerotic metastasis. The initial symptom in each case was sciatic pain. In both cases the diagnosis was confused with that of Paget's disease because of the failure, at first, to interpret properly the roentgenographic data.

The authors concluded that carcinoma of the prostate gland may exist with relatively few symptoms and slight, if any, enlargement of the gland, and result in generalized osseous metastasis with almost no other involvement. Once metastasis occurs in bone it apparently proceeds through the skeleton progressively, and independently of either the blood stream or the regional lymph nodes. Even though there may be almost general involvement of the bone marrow by metastatic deposits, the anemia is not necessarily severe.

Barringer<sup>46</sup> stated that little is known concerning the etiology of carcinoma of the prostate gland, and in only a small percentage of cases is the diagnosis made sufficiently early to give any type of treatment a fair chance of success. Even if an early diagnosis is made there is no general agreement as to the best way to treat the neoplasm. Barringer attempts to analyze the reasons for the failures of the past, to consider the present ideas on the subject and to suggest further improvement in the control of the disease by irradiation.

The age incidence in cases of carcinoma of the prostate gland does not vary greatly from that of benign hypertrophy. Young, in a series of 898 cases of benign hypertrophy, showed that 794 (88.4 per cent) occurred between the ages of 50 and 75 years. In Barringer's series of 280 cases of carcinoma of the prostate gland, 197 (86.6 per cent) were within the same age group. According to Young, the peak age group for benign hypertrophy occurs at from 55 to 59 years. The peak age group for carcinoma in Barringer's series is from 65 to 69 years.

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45. O'Crowley, C. R.; Trubek, M., and Goldstein, H. H.: Osseous Metastasis in Carcinoma of the Prostate, *J. Urol.* **26**:665 (Nov.) 1931.

46. Barringer, B. S.: Carcinoma of the Prostate, *Ann. Surg.* **93**:326 (Jan.) 1931.

The symptoms of carcinoma of the prostate gland are not easily distinguished from those of benign hypertrophy, for both conditions are often present at the same time. Carcinoma of the prostate gland is frequently superimposed on benign hypertrophy, but many carcinomas also develop in nonhypertrophied glands. An earlier diagnosis usually is made if the neoplasm develops subsequent to benign hypertrophy. Urinary symptoms are usually the first observed by the patient and the most significant from the point of view of early diagnosis. The two most common symptoms occurring early in the disease are frequency and difficulty of urination. In 82 per cent of the 280 cases these were the first symptoms noticed.

The significance of early diagnosis is reiterated. On the average twenty-four months elapsed between the onset of symptoms and the establishment of the diagnosis in the series. The persistent exhibition of frequency, difficulty in urination, nocturia and retention among patients of carcinoma age requires careful and painstaking search for carcinoma of the prostate gland.

An estimate of 241 of 280 cases of this series showed that 221 were classified as advanced cases and only 20 were designated as in the early stages. Seventy-eight of the 221 represented postoperative recurrences. Five of 46 patients suffering from the advanced type of disease are alive and well after five years. These patients were treated by the insertion of steel radium-bearing needles through the perineum into the prostate gland and seminal vesicles. Small doses, from 200 to 300 millicurie hours for each needle, were used, the dose being repeated every two or three months until the condition was controlled or until no evidence of regression was found. Since the first series of carcinomas of the prostate gland the treatment has had to be changed frequently in order to take advantage of the newer methods and agents. Glass seeds of radon, low voltage and then high voltage roentgen rays, the radium element pack, radon filtered by platinum and gold seeds of radon have all been used alone and in various combinations. In spite of the continual transition of irradiation, 8 of 40 patients have been alive and well for periods of more than five years, or 20 per cent of the active cases are still under control after five years as compared with 10.8 per cent in the first reported series.

[COMPILERS' NOTE.—The fact that twenty-four months elapsed between the onset of symptoms and the establishment of diagnosis reveals the inadequacy of methods of detecting this fatal disease. It is interesting to note that Barringer obtained such good results from transperineal irradiation with needles. Bumpus, several years ago, discarded the method after showing little difference in results in a series of cases in which the treatment was used as compared with a series in

which treatment was not given. Recently the development of biopsy by means of an aspirating needle has been described, and it is hoped that this method of diagnosis may lead to earlier recognition of the disease with improvement in end-results from immediately applied intensive treatment.]

Mulholland <sup>47</sup> stated that since it is well known that cellular elements are found in secretions that accompany malignancy, the natural inference would be that the prostatic secretion might contain a cellular element that is diagnostic of carcinoma of the prostate gland. An attempt was made to become familiar with the characteristic appearance of secretion from the prostate gland when malignancy was known not to be present. Examination was then made of smears of the secretion from the gland in 30 cases of carcinoma. A different element was soon noted. There was a cell that was about 2 or 3 times the size of an ordinary polymorphonuclear leukocyte. It tended to occur in clumps and many times the cells appeared to have been packed together, causing marked variation in cellular outline. The nucleus in all well stained sections was acidophilic, and contrasted with the basophilic staining of the polymorphonuclear cells. These cells were present in 23 (77 per cent) of the 30 patients examined.

MacCarty <sup>48</sup> stated there are 2 types of growth of the prostate gland which are unquestionably carcinomatous: the scirrhous type, which is probably not the one that gives the picture Mulholland described, and the type in which there is proliferation of cells within the acini and piling up of these cells. It is easily possible for these to be exfoliated and expressed into the urethra. The author presented examples of definitely malignant cells, some of which had been exfoliated. It is possible for the secretion of a carcinomatous prostate gland to contain some of these disintegrating cells.

*Tuberculosis.*—Patch and Foulds <sup>49</sup> stated that in tuberculosis of the genito-urinary tract the prostate gland is involved in about 80 per cent of the cases. The coexistence of hyperplasia or of adenomatous enlargement and tuberculosis is rare. Two cases in which the combination of these conditions existed were noted in the postoperative examination of 491 prostate glands, and are reported together with 14 obtained from the literature. In only 1 case was the diagnosis suggested before operation, although tuberculosis was present in the genital tract or elsewhere

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47. Mulholland, S. W.: A Study of Prostatic Secretion and Its Relation to Malignancy, Proc. Staff Meet., Mayo Clin. 6:733 (Dec. 16) 1931.

48. MacCarty, W. C., in discussion on Mulholland (footnote 47).

49. Patch, F. S., and Foulds, G. S.: Tuberculous Infection of the Adenomatous Prostate, Brit. J. Urol. 3:269 (Sept.) 1931.

in the body in 50 per cent of cases. In 2 instances there was fairly conclusive proof at necropsy of primary tuberculosis of the prostate gland. The occurrence of tuberculosis with enlargement of the prostate gland had no effect on the postoperative course in 8 cases. In 6 cases the convalescence was prolonged because of inflammatory complications and persistent fistulas. In 2 cases death occurred soon afterward. The presence of tuberculosis is no contraindication to the removal of an enlarged prostate gland that is definitely obstructive; in such cases, all methods of treatment, general or local, which are of value in any type of tuberculosis should be used.

#### TESTES, EPIDIDYMIS AND SEMINAL VESICLES

*Tumor of Testis.*—Rea<sup>50</sup> analyzed 76 cases of malignancy of the testes. In 65 cases the testes were descended and in 11 (14 per cent) they were undescended. In 6 of the latter cases the testes were in the abdomen. The condition appeared in most cases between the ages of 20 and 40 years. The duration, in 55 per cent of the cases, was less than one year in the first group, and there were as many tumors of more than two years' duration as there were of less than two years' duration in the second group. Trauma was noted in 38 per cent of the cases.

Rea concluded that malignancy of the testis is uncommon, but it occurs relatively more frequently in undescended than in descended testes. There is as much danger of malignancy in the abdominal as in the inguinal testis. The various methods of treatment as carried out at present are unsatisfactory. In early cases in which the diagnosis is doubtful, biopsy and frozen section should be done, with the patient prepared for immediate radical operation in case it should be necessary. The undescended testis should be placed in the scrotum in all cases; if this is impracticable, it should be excised, provided the opposite organ is normally placed or placeable. Approximately 13 per cent of patients survive four years after orchidectomy. When suitable irradiation is used in conjunction with orchidectomy, this percentage is increased if there is no obvious metastasis. About 7 per cent of patients who manifest metastasis are at least temporarily saved by irradiation. The value of Coley's serum used with other methods requires further study. The best results from any single method in the operable cases were obtained from block excision of the testis, spermatic cord and regional lymph nodes. From a review of the literature it would seem that better results follow the combined use of radical operation and irradiation.

50. Rea, C. E.: Malignancy of the Testis, with Special Reference to Undescended Testis: Report of 76 Cases (17 Cases Previously Reported). *Am. J. Cancer* **15**:2646 (Oct.) 1931.

Hady<sup>51</sup> reported a case of chorio-epithelioma of the testis of a man aged 22. For eight years he had had an inguinal hernia, which had disappeared four months previously. At that time the corresponding testis had begun to enlarge. Operation was refused until cough and increasing weakness forced the patient to go to the clinic, where the right testis was removed. A week later rhythmic convulsive movements began in the arm, and examination revealed several subcutaneous tumors and a sanguineous exudate in the pleural cavity. Death followed soon afterward. Necropsy was not done.

The extirpated tumor measured 9 by 6 by 5 cm., and was soft and smooth. Cross-section showed a white, caseous surface with a large hemorrhagic area. Microscopic sections of the hemorrhagic area showed deposits of fibrin with structures suggesting chorionic villi, with great variations in size and staining reactions of the cells. In other areas the cells grew in narrow strips and contained vacuoles of great size. The diagnosis was chorio-epithelioma of the testis.

The clinical history with the type of metastasis and the tendency to hemorrhage, as well as the histologic picture, was so suggestive of chorio-epithelioma that the Aschheim-Zondek test was studied when the patient was in the hospital. In the first series of tests with 10 mice, 2 groups of mice were used, one in which the weight of the animals varied from 4.5 to 5.6 Gm., and the other in which the weights were from 5.8 to 8.5 Gm. In the first group, probably due to the low weight, only reactions I and II were obtained, whereas in the second group reactions I, II and III were strongly positive. In the second test, ten days later, the reaction was completely positive in all 3 female mice, and the testes and seminal vesicles of 3 male mice were swollen, as described by Brouha and Simonet.

Loubat and Dareys<sup>52</sup> reported the case of an infant aged 15 months, with enlargement of the scrotal contents to about 20 cm. in diameter. The clinical diagnosis of mixed tumor of the testis was made, and the tumor was removed at operation. Gross examination showed that the testis and epididymis took no part in the formation of the tumor. These organs were atrophic and pushed to one side by the large, solid tumor. The latter evidently took its origin from the tunica vaginalis. The structure of the tumor was that of fibromyxosarcoma. Six similar cases from the literature were also reported.

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51. Hady: Chorionepitheliom beim Manne mit Stark positiver Aschheim-Zondekscher Schwangerschaftsreaktion, *Zentralbl. f. Gynäk.* **55**:912, 1931; abstr., *Am. J. Cancer* **15**:3040 (Oct.) 1931.

52. Loubat and Dareys: Les tumeurs para-testiculaires chez l'enfant, *Gaz. hebdl. d. sc. méd. de Bordeaux* **52**:184, 1931; abstr., *Am. J. Cancer* **15**:3041 (Oct.) 1931.

Keijer<sup>53</sup> reported 2 cases of seminomas of the testis which were removed surgically and also treated by roentgen rays. Abdominal metastasis occurred in 1 case. Both patients are living and well nine years after operation. A case of teratoma of the testis was also reported; death followed removal of the testis and roentgenotherapy. Apparently teratomas are influenced so little by roentgenotherapy that it is questionable whether it should be given diffusely over the abdomen, although good results are usually obtained in cases of the seminoma group.

Keijer operates immediately in these cases so that a definite diagnosis may be made. If metastasis is evident, operation should not be done. If the tumor is a seminoma, roentgenotherapy is given to the abdomen, especially in cases in which metastasis cannot be demonstrated. If the tumor is a malignant teratoma, the roentgenotherapy may be eliminated.

Seminomas of the ovary have been observed. Keijer reported 2 cases of tumor of the ovary, one in a girl aged 18 years and the other in a girl aged 13 years. A pathologic diagnosis of seminoma in one instance and teratoma in the other was made after removal of the growth. The histologic examination usually determines the prognosis. As in the cases of tumors of the testis, the best results are obtained with the seminomas.

*Torsion of Appendages.*—Dix<sup>54</sup> reviewed from the literature 51 cases of torsion of the appendages of the testis and epididymis, and added 2 of his own cases; 48 of these were of the testicular appendix. This condition should be recognized as a possible lesion in obscure cases of subacute epididymo-orchitis in infants and adolescents. It occurs usually before or at puberty and affects each side with equal frequency. The onset is sudden, with pain from the testis radiating along the cord, and with swelling of the scrotum and tenderness. If these symptoms occur in an adolescent and there is no specific cause of epididymo-orchitis, the diagnosis is not difficult. The symptoms are not as severe as in torsion of the testis; since the treatment of both conditions is surgical, the distinction prior to operation is not important.

The cause of the condition has not been determined. Many observers state that it is not associated with trauma or strain. Immediate operation is indicated because it relieves the pain and shortens the illness, and in the case of incorrect diagnosis the palliative treatment of torsion of the testis is possible. At operation the appendix is enlarged, twisted on its pedicle, edematous and discolored, depending on the degree of strangulation. In the late cases there may be inflammatory adhesions to the surrounding structures.

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53. Keijer, S.: *Bestrahlung des Seminoms von Testis und Ovarium*, Nederl. tijdscher v. geneesk. **2**:5566, 1930; abstr., *Ztschr. f. urol. Chir.* **32**:217 (June 26) 1931.

54. Dix, V. W.: *On Torsion of the Appendages of the Testis and Epididymis*, *Brit. J. Urol.* **3**:245 (Sept.) 1931.

## URETHRA

*Tumors.*—Meyer<sup>55</sup> stated that tumors of the deeper layers of the wall of the urethra form a special group which is to be distinguished from tumors of the urethral mucosa. The tumors of the deeper layers are recognized by their more cellular, fibrous centers and their sharp demarcation from the mucosa. The mucosal polyps have a rather loose, fibrous framework and a striking number of large thick-walled vessels.

Three cases of tumor of the deeper layers of the wall of the urethra were reported. The first was a fibroma about 1.5 cm., with a papillomatous proliferation of the overlying epithelium. It arose from the right lateral wall of the urethra, near the meatus. The patient was a woman aged 36. In the second case, that of a woman aged 31, the fibroma arose from the anterior wall of the urethra, in the space between the urethra and the clitoris. This also had a papillary covering, chiefly of squamous epithelium. In the third case, there was a tumor about 2.5 cm. in diameter with a pedicle, situated between the meatus and clitoris and consisting of muscular tissue covered by papillae of stratified squamous epithelium.

Two cases of congenital polyps of the urethra were mentioned. The first was found in a premature female fetus, 40 cm. in size, as a tiny tumor with a 14 mm. pedicle arising in the upper part of the urethra but projecting from the meatus. The second polyp was similar; it arose from the upper part of the urethra by a long pedicle. It was found in a new-born boy with hypospadias and hypoplastic genitalia.

[COMPILERS' NOTE.—Fibromas or fibromyomas occur more commonly in the female urethra than in the male. They may be attached to any part of the urethra but usually to the posterior half. They are generally covered with urethral mucosa, and cause few symptoms. They are unattached to the periurethral tissues and shell out readily at operation. They may grow rapidly and become very large; as a rule, they are attached to the urethra by a pedicle.

Small polyps or papillomas of the urethra are often found. They are the result of long and tedious infection of the urethra. They have little clinical significance. Both the large and small polyps respond readily to fulguration or snaring. Multiple and extensive growths are occasionally seen, and in some cases may cause almost complete obstruction.]

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55. Meyer, Robert: Zur Kasuistik der Fibrome, Myome, und kongenitalen Polypen der Harnröhre, *Zentralbl. f. Gynäk.* 55:917, 1931; abstr., *Am. J. Cancer* 15:3038 (Oct.) 1931.



*Caruncle*.—Deming<sup>56</sup> stated that large and extensive caruncles should be treated by a thorough surgical procedure which removes the whole tumor-bearing area rather than by simple surgical excision, radium, electric coagulation or caustics. Eight cases are reported in which complete relief was obtained by radical urethroplasty. There were no complications following the operation, and drainage of the urethra by catheter was unnecessary.

[COMPILERS' NOTE.—Deming's article indicates that he has had good results with urethroplasty. In most cases, particularly those of the smaller caruncles, excellent results are obtained by complete fulguration of the growth, which can usually be done at one sitting. The earlier method of repeated topical applications of caustics causes considerable discomfort and is usually time-consuming and unsatisfactory.]

#### PENIS

*Carcinoma*.—Buschke and Loewenstein<sup>57</sup> reported a case of carcinoma of the penis of a man aged 50. Seven weeks before observation the dorsum of the penis was burned with hot fat. Small warts arose about the periphery of the vesicular burn, followed rapidly by the development of a large, cauliflower-like tumor. Biopsy showed an anaplastic infiltrating carcinoma. Since the site of the burn was the same as that of a previously existing pointed condyloma, it was recorded as carcinoma arising on condyloma. A case of Israel's in which carcinoma arose in the scar after removal of a condyloma is cited.

Guillera<sup>58</sup> reported 11 cases of carcinoma of the penis which were observed for a year and a half; 7 of the 11 patients had phimosis. The primary lesion was treated with radium in 9 cases; amputation of the penis by electrocoagulation was done in 2 cases owing to the extent of the lesions. When the invasion extends to the root of the penis, conservative treatment is not advisable; even if it is successful, it will leave only a useless stump. In less advanced, and especially in incipient, cases radium is to be recommended, particularly for young patients. In circumscribed growths, even if they are deeply infiltrating, amputation is unnecessary. If amputation finally becomes imperative on account of failure of radium treatment, conservative amputation is not advisable.

56. Deming, C. L.: A New Surgical Procedure for the Treatment of Resistant Urethral Caruncles, *New England J. Med.* **205**:484 (Sept. 3) 1931.

57. Buschke, A., and Loewenstein, Ludwig: Beziehungen der spitzen Kondylome zu den Carcinomen des Penis, *Arch. f. Dermat. u. Syph.* **163**:30, 1931; abstr., *Am. J. Cancer* **15**:3039 (Oct.) 1931.

58. Guillera, L. G.: Tratamiento del cáncer del pene, *Ecos españ. de dermat. y sifil.* **6**:90, 1930; abstr., *Am. J. Cancer* **15**:3038 (Oct.) 1931.

In one of the cases the upper part of the glans was destroyed. The other cases were of the vegetative type, some with enormous carcinomatous proliferations. Six of 9 patients died as the result of visible metastasis in the glands, pubis and perineum. There has been no evidence of recurrence for two years in one case, and for one and a half years in the other. In the 11 cases there were 3 cures (27 per cent). In these cases there had been the least clinical invasion, and operation had not been performed.

#### URINARY INFECTIONS

Nyberg<sup>59</sup> described the use of bacteriophage in acute and chronic cases of pyelitis caused by infection with the colon bacillus. Three patients with acute pyelitis were completely cured. The results were not so definite in the chronic cases, which may be due to the fact that effective bacteriophages are difficult to find and more than 1 type of colon bacillus frequently occurs, each type reacting only to its own bacteriophage. In 1 of the chronic cases in which the best results were obtained, there had been pyelitis from the colon bacillus for three years. Three different types of colon bacilli were cultured from the urine. Treatment by bacteriophage gave good results, and 2 types of colon bacilli disappeared from the urine. A bacteriophage for the remaining individual strain of colon bacillus could not be found.

Cabot<sup>60</sup> studied a large group of cases, in most of which operations had been performed directly on the kidney, but in a few only cystoscopic investigations had been carried out, with a view to determining whether it is possible to show the existence of principles that may guide in the treatment of postoperative or postcystoscopic fulminating infection of the kidney. In most of the cases considered severe infection followed.

These fulminating infections apparently occur almost solely in kidneys that are known to be the seat of infection; they are not clearly related to the amount or duration of the infection, but rather to the injury of the kidney, to the infecting organism and to the resistance of the patient. They are usually due to various cocci, of which the staphylococci are an important group, and rarely, if ever, to the colon bacillus. The character of the reaction is influenced by the rapidity of absorption due to the large supply of blood and lymph to the kidney.

These fulminating infections appear as a severe infection associated with a disproportionate rise in the pulse rate accompanying and often

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59. Nyberg, Carl: Die Bakteriophagenbehandlung der Coli-Pyelitis, *Duodecim* **46**:775, 1930; abstr., *Ztschr. f. urol. Chir.* **32**:220 (June 26) 1931.

60. Cabot, Hugh: Discussion of the Treatment of Acute Postoperative Renal Infections, *Proc. Staff Meet., Mayo Clin.* **6**:755 (Dec. 23) 1931.

exceeding the increase in temperature. If the kidney on the opposite side is of reasonably good functional value, removal of the injured kidney at a certain time may save life. As to whether nephrectomy should be performed, the errors of judgment have most frequently occurred on the side of too long delay. The margin of safety is within narrow confines, sometimes limited to a matter of hours. The question of nephrectomy will usually present itself between the second and fourth day. A steadily rising pulse rate, which in adults as a rule will be 120 or more, is the most significant single indication that there are complications. If this increased pulse rate is associated with nausea, vomiting, or hiccup, the indication becomes more definite. Hourly or half hourly recording of the pulse rate, as in cases of suspected concealed hemorrhage, is helpful. In cases in which diagnosis is doubtful the safer procedure would be nephrectomy, since the condition will probably be fatal if the appropriate time for this operation is passed.

The avoidance of infections aggravated by surgical operations is more important than treatment. The kidneys should be handled gently, the substance of the kidney should not be torn in removal of a stone, and nephrotomy should be adopted for the extraction of stones deeply placed in the kidney which will cause laceration of tissue if they are dragged into the pelvis. Drainage of the kidneys by nephrostomy in order to avoid possible distention from temporary obstruction of their outlets during the early days of convalescence is also important. Examination of a series of cases at the Mayo Clinic disclosed that convalescence has been significantly freer from febrile reactions in the presence of temporary nephrostomy.

[COMPILERS' NOTE.—The principles of urologic surgery advocated by Cabot are sound. Certainly no group of cases calls for more meticulous judgment in deciding for or against nephrectomy than those under consideration. Recently Nesbit of the University of Michigan sounded a more conservative note, stating that most acute staphylococcal infections tend to run a stormy although self-limited course. This author believes that operation is seldom indicated unless complications such as perinephritic abscess or possibly carbuncle arise. However, as Cabot stated, the margin of safety is within narrow confines and the study of the patient's clinical course as to temperature, pulse and symptoms should guide the surgeon in deciding on nephrectomy. Certainly his emphasis on care not unduly to traumatize kidneys by operative procedures in the presence of infection and to establish proper drainage is not to be taken lightly.]

Fisch<sup>61</sup> reported that as long as there is pus in the urine microbes will be present except for short intervals; even though the pus becomes amicrobic, infection will undoubtedly recur. During the time between infections, if the microbe was other than the Koch bacillus, no changes will be found in the leukocytes, which are few in number. If a few microbes are present, their form will be attenuated, so it is difficult to find them. In pyuria produced by the bacillus of tuberculosis, the leukocytes are altered; they have been affected by the causticity of their milieu, they are opaque, their nucleus is scarcely visible and they have the appearance of cooked cells. If leukocytes having these characteristics are found in amicrobic pus, the Koch bacillus is still present, as will be revealed by repeated, careful examinations. The pus of tuberculosis owes its existence solely to the Koch bacillus and will be found in such cases even though the pus in the urine appears amicrobic.

The apparent disappearance of microbes from the pus after abundant hematuria is due to the defensive power of the blood, which has prevented temporarily proliferation of the microbes. The secretions of the Koch bacillus contain certain toxic substances which have a selective action on the tissues treated with tuberculin; they are caustic and alter the tissues of the bladder, producing ulcerations and more or less copious hemorrhage. They have a harmful effect not only on the bladder but also on its content, so that the urine becomes pale and colorless, and the leukocytes are different from those coming from nontuberculous surroundings. The only amicrobic pyuria that is of interest is the frank amicrobic pyuria of tuberculosis, and its causative agent will always be found after persistent search.

[COMPILERS' NOTE.—In 1906 Colombino called attention to the phenomenon mentioned. Albarran, Legueu, Chevassu and others of the Necker school have also pointed out this important fact in the early diagnosis of renal tuberculosis. It is the general opinion of urologists at present that a diagnosis of renal tuberculosis must be based on more definite data, such as a positive pyelogram, diminution of the renal function and the presence of Koch bacillus in the urine. Since the time of Albarran it has been known that the presence of Koch's bacillus in the urine does not always indicate renal tuberculosis. In many instances the bacillus of tuberculosis may be excreted in the urine without having produced any other anatomicopathologic lesion than that of tuberculous nephritis, which may be caused by tuberculous bacilluria. These amicrobic pyurias, although useful as an aid in diagnosis, are not sufficient of themselves to permit a definite diagnosis of urinary tuberculosis.]

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61. Fisch, J.: Pyuria amicrobienne, *J. d'urol.* **32**:113 (Aug.) 1931.

## UROGRAPHY

Viethen <sup>62</sup> stated that intravenous urography is of especial significance in pediatrics, as iopax has been found to be tolerated well by nursing infants and small children. A dose of 25 cc. may be given to nursing infants, and from 30 to 40 cc., and even 60 cc. of the 40 per cent solution may be given to small children and school children. If the child is very young, injections are best made in the external jugular vein and not in the longitudinal sinus. The most satisfactory pictures of the renal parenchyma are obtained immediately after injection. Quantitative estimation of the iodine in the urine shows that more than 90 per cent is eliminated from five to ten hours after injection. Tests of renal function and retrograde pyelography should not be neglected.

Viethen <sup>63</sup> reported on 112 cases in which pneumoroentgenography was done. Some cases were unilateral, others bilateral; in certain cases the procedure was combined with pyelography. Rosenstein's technic was used because of its safety. An oxygen embolism was noticed in one case, but the patient returned to normal within two hours and did not feel any ill effects.

In cases of tumor or tuberculosis this procedure has been of value in differential diagnosis. Complications may almost always be avoided by adhering closely to Rosenstein's technic. The most serious complication that might occur is that of oxygen embolism usually resulting from puncture of a blood vessel. This may be avoided if the needle is tested for blood before the oxygen is injected. The author uses a fixed metal guard plate for the needle so as to eliminate the possibility of inserting the needle too deeply. Good results are generally obtained in cases of tumors, tuberculosis and renal aplasia. The method is contraindicated in cases of perinephritic abscess.

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62. Viethen, A.: Intravenöse Urographie im Kindesalter, *Ztschr. f. Kinderh.* **50**:141, 1930; abstr., *Ztschr. f. urol. Chir.* **32**:183 (June 26) 1931.

63. Viethen, Herman: Technik und Indikationsstellung der Pneumoradiographie des Nierenlagers, *Ztschr. f. Urol.* **25**:1, 1931; abstr., *Ztschr. f. urol. Chir.* **32**:177 (June 26) 1931.

# ARCHIVES OF SURGERY

VOLUME 25

SEPTEMBER, 1932

NUMBER 3

## GASTRIC SECRETION

### I. A TRANSPLANTED SUBCUTANEOUS GASTRIC POUCH

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Most of the mechanism of the secondary phase of gastric secretion still remains a fascinating mystery. One knows the site of origin of the secretory stimulus and something of its transmission to the secreting cells, but that is nearly all. Yet this phase of secretion is of great importance not only to the physiologist, but to the surgeon, for it plays an important part in the results obtained following modern surgical procedures on the stomach.

There are three stages of gastric secretion, the primary, the secondary and the intestinal. The primary is also known as the vagal, the psychic or the cephalic. Its purpose is to stimulate the flow of gastric juices so that they can act on the food and by digestion produce chemical substances that initiate and carry on the second phase. The primary phase follows a psychic or sensory stimulus, such as the thought of food or seeing, smelling, tasting or chewing food. In different persons there are variable responses, some people tending to have a consistently high rate of secretion and others a low one. The secretory response also varies at different times in the same person. In hunger it tends to be large, and in satiety, small or absent. There is a latent period of about five minutes before the secretion commences, and it persists for from one to three hours after the end of the stimulus. The secretory impulse is transmitted to the stomach over the vagi. Experimental section of these nerves permanently abolishes it. To recapitulate, the mechanism of the primary phase is neurogenous, the afferent channel commencing at one of the sensory organs, such as taste, and the efferent pathway being the vagi.

#### THE SECONDARY PHASE OF GASTRIC SECRETION

*The Stimulating Substances.*—The secondary secretion begins after food enters the stomach. The stimulus for this phase is almost entirely chemical. Among the chief chemical stimulants are the end-products of protein digestion, meat extracts, vegetable juices and water; also the

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From the service of Dr. A. A. Berg and the Department of Laboratories of the Mount Sinai Hospital.

saliva, the bile and the pancreatic juice. It is therefore seen that the secretion resulting from the primary phase by digestion of meat and other foods liberates products that furnish the stimulus for the secondary phase. Furthermore, substances present in the gastro-intestinal tract that can readily reach the stomach (such as saliva, by swallowing, and bile and pancreatic secretion, by regurgitation) may also produce the secondary secretion. But the manner of action of these chemical excitants has not been cleared up, although a great deal of knowledge on the subject has been accumulated.

*The Site of Stimulation.*—The glands secreting acid and pepsin are situated in the body and fundus of the stomach, constituting about the proximal four-fifths. The antrum or distal fifth secretes an alkaline mucus and possibly a weak proteolytic ferment. One would expect that the chemical stimuli for the secondary phase would act on that

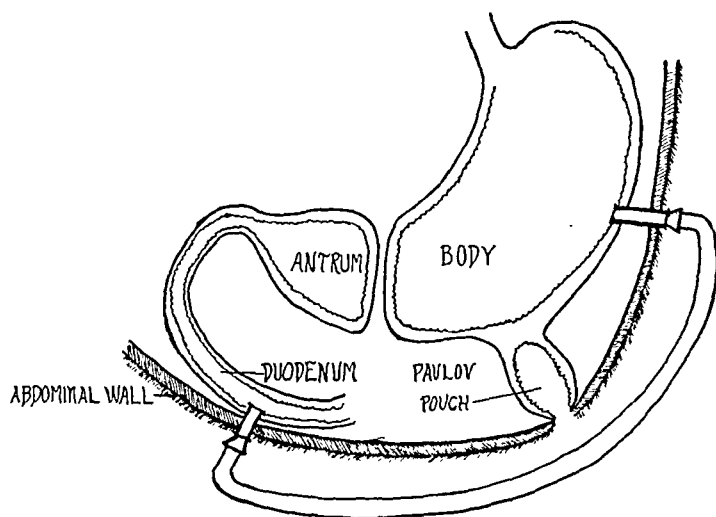


Fig. 1.—Type of stomach prepared by Gross (Arch. f. Verdauungskr. **12**:507, 1906).

portion of the stomach that contains the acid and peptic cells. Yet experimental findings show that this is not true. A dog's stomach prepared according to the manner illustrated in figure 1 shows the following: (1) a Pavlov pouch<sup>1</sup> from which the secretions are collected, (2) a separation of the antrum from the body and the fundus and (3) fistulas into the duodenum and into the fundus. When the animal is not used experimentally these fistulas are connected externally by a rubber tube and form an external gastroduodenostomy passage. If any of the usual chemical excitants, such as meat or meat extracts, are

1. A Pavlov pouch is one prepared from the greater curvature of the stomach in such a way that only a mucous membrane septum separates it from the interior of the stomach. It reflects the secretory activity of the stomach and through a fistula opening on the exterior permits the collection of pure gastric juice without admixture of food.

placed in the fundus of such an animal, secretion of acid or pepsin does not follow.<sup>2</sup> Chemical stimulation of the body and fundus does not produce the secondary secretion.

If, on the other hand, a dog is prepared as shown in figure 2, quite different results may be obtained. Here (1) the antrum has been separated from the body of the stomach and, from the duodenum and the antral pouch, communicates with the exterior by means of a fistula, and (2) another fistula has been made into the body of the stomach. The continuity of the gastro-intestinal tract has been reestablished by a gastro-enterostomy. If chemical excitants are placed in the pyloric part secretion results.<sup>3</sup> The chemical stimulus for the secondary secretion, therefore, acts through the antral portion of the stomach.

The natural question, of course, is, how is the stimulus transmitted from the antrum to the cells of the body and fundus? There are two

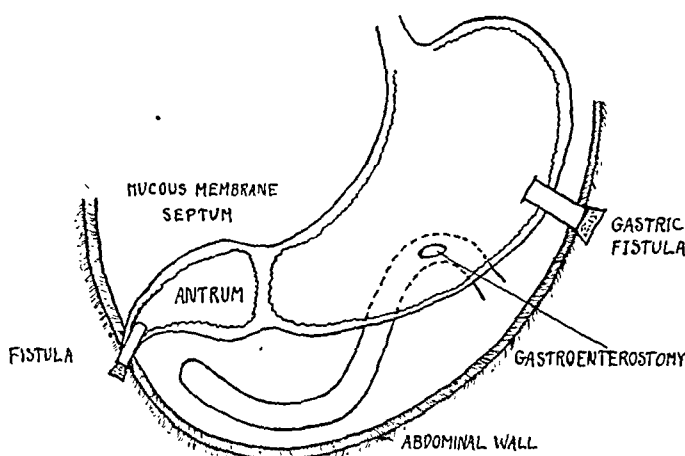


Fig. 2.—Type of stomach prepared by Sawitsch and Zeliony (footnote 3, first reference).

possible ways: (1) through the nerves and (2) through the blood stream.

*Possible Nerve Channels.*—There is no definite proof that the vagi transmit secretory stimuli from the antrum to the fundus. There is, however, evidence that normal vagi are necessary for a normal

2. Gross, W.: Beitrag zur Kenntnis der Sekretionsbedingungen des Magens nach Versuchen am Hund, *Arch. f. Verdauungskr.* **12**:507, 1906. Zeliony, G. P.: Contribution à la physiologie des glandes stomacales, *Arch. d. sc. biol.* **17**:425, 1913.

3. Sawitsch, W., and Zeliony, G.: *Arch. f. d. ges. Physiol.* **150**:128, 1913. Lönnquist, B.: Beiträge zur Kenntnis der Magensaftabsonderung, *Skandinav. Arch. f. Physiol.* **18**:194, 1906. Gross (footnote 2, first reference). Ciminata, A.: La secrezione del fundus dello stomaco provocata da stimoli chimici applicati sulla mucosa della pars pilorica, *Arch. di fisiol.* **23**:221, 1925. Lim, R. K. S.; Ivy, A. C., and McCarthy, I. E.: Contributions to the Physiology of Gastric Secretion by Local (Mechanical) and Chemical Stimulation, *Quart. J. Exper. Physiol.* **15**:12, 1925.



secondary secretion. Thus, section of both vagi not alone abolishes the entire primary secretion, as was mentioned, but also markedly diminishes the secondary secretion. This is shown in the experiments of Orbeli.<sup>4</sup> He prepared a dog with a Pavlov pouch and a gastric fistula. Food was placed directly in the stomach through the fistula in order to eliminate the primary phase of secretion. The secretion recovered from the Pavlov pouch was therefore due entirely to the secondary phase. Then the vagi were sectioned and the same experiment was performed. There followed a marked reduction in the quantity of the secretion. The reason for this drop is not clear. The possible explanations would appear to be (1) that part of the secondary stimulus from the antrum to the secreting cells of the fundus reaches these cells over the vagus nerves, (2) that the secondary secretion is chiefly humoral, but that the chemical excitants in the blood act partly on the vagus nerve endings, or (3) that the vagus nerve maintains a state of trophic tone in the secretory cells which is necessary for their best function. At any rate, we may say that the intact vagus nerve appears to be necessary for the proper maximum function of the secondary phase.

But it will be noted that, even after the section of the vagi, the secondary phase persisted, and this suggests, of course, that a stimulating substance is carried through the blood from the antrum to the fundic glands. Can such a substance be demonstrated in the blood stream?

The earliest experiments to determine the presence of a humoral stimulant were performed by Edkins. They were suggested by the fact that a pancreatic secretin was absorbed into the blood stream from the intestine and carried to the pancreas. Edkins<sup>5</sup> reported that an extract could be prepared from the antrum of the stomach, which after intravenous injection produced a gastric secretion. He called this substance gastrin. There followed a large series of experiments by a number of observers showing that extracts not only of the stomach but of the intestine and of other organs produced a secretion from the stomach after subcutaneous, intramuscular and intravenous injections.<sup>6</sup>

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4. Orbeli, L. A.: De l'activité de glandes à pepsine avant et après la section des nerfs pneumogastriques, *Arch. d. sc. biol.* **12**:71, 1906.

5. Edkins, J. S.: The Chemical Mechanism of Gastric Secretion, *J. Physiol.* **34**:133, 1906.

6. Popielski, L.: Ueber die physiologische Wirkung von Extrakten aus sämtlichen Teilen des Verdauungskanal (Magen, Dick- und Dünndarm), sowie des Gehirns, Pankreas und Blutes und über die chemischen Eigenschaften des darin wirkenden Körpers, *Arch. f. d. ges. Physiol.* **128**:191, 1909. Maydell, E.: Zur Frage des Magensekretins, *Arch. f. d. ges. Physiol.* **150**:390, 1913. Keeton, R. W., and Koch, F. C.: The Distribution of Gastrin in the Body, *Am. J. Physiol.* **37**:481, 1915. Tomaszewski, Z.: Ueber die chemischen Erreger der Magendrösen, *Arch. f. d. ges. Physiol.* **170**:260, 1918. Popielski injected extracts from gastro-intestinal and other organs intravenously. Maydell injected antral extracts subcutaneously. Keeton and Koch found extracts of the stomach and duodenum to be potent.

These experiments show without question that tissue extracts of many kinds, injected parenterally and reaching the stomach through the blood stream, produce gastric secretion. However, it does not necessarily follow that such a mechanism is involved in normal gastric digestion.<sup>7</sup>

In order to throw more definite light on this subject, Lim,<sup>8</sup> and later Ivy<sup>9</sup> and his co-workers, performed cross-circulation experiments, in which the blood of a fed animal was carried over into a hungry one. They could not demonstrate to their satisfaction that gastric secretion resulted in the second animal. But Rasenkov,<sup>10</sup> using a different transfusion technic, was later able to show that substances that stimulate the stomach to secrete both hydrochloric acid and pepsin can thus be transmitted.

About the same time, Ivy and Farrell<sup>11</sup> succeeded in transplanting into the mammary gland a pouch prepared from the greater curvature of the stomach. The operation was done in two stages. In the first, the pouch was sewed into a bed prepared in the mammary gland, and the blood vessels to the pouch were left intact. From two to four weeks after the first operation, the blood vessels were severed. In this way they obtained a pouch with the extrinsic nerves completely severed and with a new peripheral circulation. They were able to show that after a meal secretion was produced in the pouch. The stimulus could have reached the pouch only through the blood.

There is therefore definite evidence that following the ingestion of food some substances are transmitted through the blood stream to the fundic glands and produce gastric secretion. It has been shown in the foregoing statements that the site of stimulus for the gastric or sec-

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7. There are several theories that assume that substances produced in the tissues of the body are responsible in part for gastric secretion. Thus Bickel (*Ergebn. d. Physiol.* **24**:228, 1925) expressed the belief that a continuous secretion would occur because of these substances, but that inhibitory impulses through the nerves interrupt it. Krimberg (*Biochem. Ztschr.* **157**:187, 1925) advanced the theory that products of muscular metabolism and also of other organs act as secretory hormones. Ordinarily these hormones do not reach the cells because of nervous interference. When this is removed, secretion results.

8. Lim, R. K. S.: A Method for Recording Gastric Secretion in Acute Experiments on Normal Animals, *Quart. J. Exper. Physiol.* **13**:71, 1922.

9. Ivy, A. C.; Lim, R. K. S.; McCarthy, J. B., and Farrell, J. I.: The Causes of Gastric Secretion with a Consideration of the Mechanism Concerned, *Am. J. Physiol.* **72**:203, 1925; **74**:616, 1925.

10. Rasenkov, I. P.: The Mechanism of the Second Phase of Gastric Secretion, *Arch. di sc. biol.* **25**:27, 1925; quoted by Babkin, B. P.: *Die Aeussere Sekretion der Verdauungsdrüsen*, ed. 2. Berlin, Julius Springer, 1928, p. 343.

11. Ivy, A. C., and Farrell, J. I.: Contributions to the Physiology of Gastric Secretion, *Am. J. Physiol.* **74**:639, 1925.

ondary secretion is the antrum. It is evident, therefore, that these humoral substances are either absorbed through or created in the antrum.

#### EXPERIMENTS

*Method.*—As a preliminary to the preparation of a modified pouch which will be reported later, several dogs were prepared by us in our laboratory with pouches similar to those used by Ivy and Farrell.<sup>11</sup> The latter had used lactating animals in order to transplant the pouches into a vascular mammary gland. As such animals were not readily available, an attempt was made to transplant the pouches into the abdominal wall. These efforts were successful. Various layers were tried, but it was found that the subcutaneous was best. A portion of the stomach along the greater curvature from 4 to 5 inches (10.16 to 12.7 cm.) long and from 1½ to 2 inches (3.77 to 5 cm.) wide was cut through (fig. 3). To this portion were usually attached three or four of the vasa brevia. The cut edges of the excised portion were approximated, a small opening being left

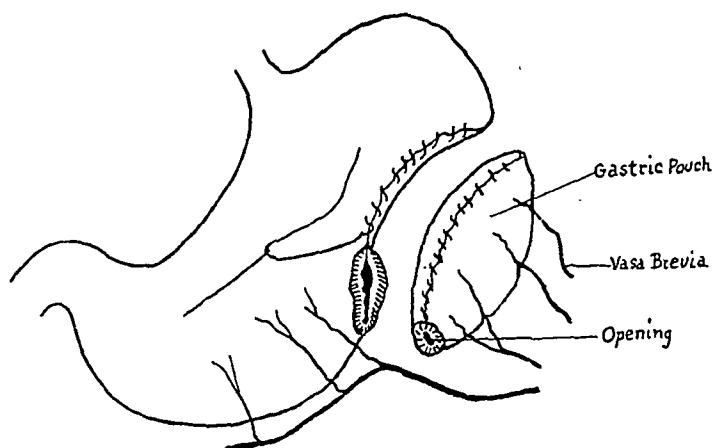


Fig. 3.—Manner of preparation of the gastric pouch from the body and fundus.

at the distal end which served as the opening of the pouch. The cut edges of the stomach were of course also approximated. The sac was then brought out of the wound, and the peritoneum and fascia were closed, except at the center, where a small opening was left through which passed the blood vessels supplying the sac. A space was prepared in the subcutaneous tissues large enough to accommodate the sac. A stab wound was made to the left of the incision, and through it the opening of the sac was drawn out. The sac was sutured to the subcutaneous tissues, as one of the difficulties encountered was its tendency to turn itself inside out.

From three weeks to three months after the first operation, the vessels to the pouch were severed through an abdominal incision on the inner side of the pouch. The longer the period permitted for the collateral circulation to establish itself, the better were the results obtained. The findings in three dogs<sup>12</sup> are reported in tables 1, 2 and 3.

12. A larger number of animals were prepared, but owing to an epidemic of distemper some of them were lost. It may incidentally be added that since the use of distemper virus on all dogs we have lost only one because of this disease. The virus was furnished us through the kindness of Mr. Edwin Berolzheimer.

*Results.*—Following the severance of the blood vessels to the pouch there is little or no continuous secretion, at the most from 0.2 to 0.3 cc. per hour. This secretion is thick mucus with no free, and a very low total, acidity.

Two hundred grams of meat and 200 cc. of water were used as a meal to stimulate gastric secretion. Following such a meal there is a

TABLE 1.—*Response of Transplanted Pouch in Dog 30 Before Severing Blood Vessels to Pouch*

Time	Quantity, Cc.	Free Acidity,* Cc.	Total Acidity,* Cc.
First hour .....	0.7	0	32
Second hour .....	1.6	0	25
Third hour .....	1.7	0	4
Fed 200 Gm. meat and 200 cc. water			
Fourth hour .....	4.77	29	72
Fifth hour .....	6.1	78	102
Sixth hour .....	9.5	82	106
Seventh hour .....	7.3	64	88
Twelve Days After Severing Blood Vessels			
First hour .....	0.2	0	+
Fed 200 Gm. meat and 200 cc. water			
Second hour .....	0.6	16	33
Third hour .....	1.1	27	54
Fourth hour .....	0.7	14	43
Fifth hour .....	0.8	25	50

\* In all the tables, free and total acidity are expressed in the number of centimeters of tenth-normal sodium hydroxide necessary to neutralize 100 cc. of gastric secretion. Toepfer solution and phenolphthalein were used as indicators.

TABLE 2.—*Response of Transplanted Pouch in Dog 52 Before Severing Blood Vessels to Pouch*

Time	Quantity, Cc.	Free Acidity, Cc.	Total Acidity, Cc.
First hour .....	0.6	0	32
Second hour .....	0.5	0	35
Third hour .....	0.5	0	
Fourth hour .....	0.0		
Fed 200 Gm. meat and 200 cc. water			
Fifth hour .....	0.7	28	43
Sixth hour .....	1.4	50	78
Seventh hour .....	1.2	58	92
Eighth hour .....	1.4	64	92
Seventeen Days After Severing Blood Vessels			
First, second, third and fourth hours.....	0		
Fed 200 Gm. meat and 200 cc. water			
Fifth hour .....	0.2	25	50
Sixth hour .....	0.3	25	33
Seventh hour .....	0.5	20	40
Eighth hour .....	0.4	25	50

definite response from the pouch. After the blood vessels to the pouch were divided there was a decided drop in the quantity of secretion and in the acidity, both free and total. As Ivy and Farrell<sup>11</sup> pointed out, the quantity of the secretion seems to be affected to a more marked degree than the acidity. This reduction may be ascribed to a diminished blood supply or to the severing of the sympathetic nerves running with the blood vessels or to both.

In these dogs free acid appeared within the first hour after feeding, showing that the latent period is little if at all prolonged. In the dogs of Ivy and Farrell,<sup>11</sup> the latent period was much longer, often several hours. The difference is possibly due to the facts that a better collateral

TABLE 3.—*Response of Transplanted Pouch in Dog 60 Before Severing of Blood Vessels to Pouch*

Time	Quantity, Cc.	Free Acidity, Cc.	Total Acidity, Cc.
First hour .....	1.3	0	28
Fed 200 Gm. meat and 200 cc. water			
Second hour .....	3.3	82	100
Third hour .....	7.3	123	133
Fourth hour .....	3.6	125	138
Fifth hour .....	5.1	119	133
Seventeen Days After Severing Blood Vessels			
First hour .....	0.1	0	+
Fed 200 Gm. meat and 200 cc. water			
Second hour .....	0.8	8	21
Third hour .....	0.9	11	23
Fourth hour .....	1.9	12	33
Fifth hour .....	1.3	12	35

TABLE 4.—*Response of Transplanted Gastric Pouch to Histamine in Dog 52 After Severing Blood Vessels, Feb. 28, 1929*

Time	Quantity, Cc.	Free Acidity, Cc.	Total Acidity, Cc.	Comment
Test July 24, 1929				
0.2 mg. histamine				
First hour.....	0.9	15	25	
Second hour.....	0.4	10	25	
Third hour.....	0.4	0	12	Mucus
Fourth hour.....	0.9	0	12	Mucus
Fifth hour.....	0.8	0	10	Mucus
Aug. 1, 1929				
0.2 mg. histamine				
First hour.....	0.6	0	15	
Second hour.....	0.4	0	25	
Third hour.....	0.4	0	15	Mucus
Fourth hour.....	0.2	0	0	Mucus
Fifth hour.....	0.2	0	0	Mucus
April 14, 1930				
0.5 mg. histamine				
First hour.....	0.5	35	60	Latent period, 15 minutes
Second hour.....	0.5	25	50	
Third hour.....	0.1	0	10	
Fourth hour.....	0.4	0		Combined pepsin of all tubes
Fifth hour.....	0.4	0		5 mm. (Mett tube)
April 30, 1930				
0.5 mg. histamine				
First hour.....	0.2	0	10	Latent period, 17 minutes
Second hour.....	1.8	50	73	
Third hour.....	0.45	90	105	
Fourth hour.....	0.25	50	65	Combined pepsin of all sam-
Fifth hour.....	0.45	0	30	ples 5 mm. (Mett tube)
Sixth hour.....	0.3	0	15	

circulation had been established in our dogs and that more blood reached the pouch. The quantity of the secretion is smallest in the first hour and then increases, usually reaching its maximum in the third hour.

*Response to Histamine.*—In table 4 is shown the response of a pouch to histamine after complete severance from the stomach of nerves

and blood vessels. As little as 0.2 mg. is at times sufficient to evoke a secretion. Five-tenths milligram always evokes it. The latent period with the latter dose is between fifteen and twenty minutes, which is almost normal. Ivy found the latent period to be much longer. Again we feel that this difference is due probably to a better blood supply for our pouches. The response to histamine is over in from three to four hours.

The significance of these results is that it is again shown that following a meal substances are passed into the blood stream that stimulate the gastric secretion of both hydrochloric acid and pepsin. These substances are responsible for at least part of the secretion of the secondary or gastric phase, and they act in the absence of the entire extrinsic nerve supply. The evidence for the belief that they reach the blood from the antral portion of the stomach has already been presented.

The nature of these substances is not clear. There are two chief theories: 1. A secretin or hormone is formed in the antrum which is then liberated into the blood stream. This would correspond with the secretin formed in the small intestine, which is carried to the pancreas. 2. The substances that are responsible for stimulation are chemical products either contained in the food or formed during digestion and absorbed through the antrum into the blood stream. They are perhaps similar in nature to histamine. While Ivy's results may have been interpreted in favor of a hormone because of the long latent period, the practically normal period in our dogs shows that this argument cannot be advanced.

The question as to the site of action of the humoral stimulant is also left unanswered. Does it act on the intrinsic plexuses or directly on the cells? This problem will be taken up in a subsequent paper.

#### SUMMARY

1. A gastric pouch transplanted into the subcutaneous tissues of the abdominal wall is described.

2. It is not necessary to use the lactating mammary gland, as Ivy and Farrell recommended, since an adequate blood supply is developed in the subcutaneous tissues.

3. Such pouches respond to the stimulation of a meal by the secretion of hydrochloric acid and pepsin. Free acid was present within the first hour.

4. Histamine in doses of 0.5 mg. or more always produces a secretion after a latent period of between fifteen and twenty minutes.

5. The results of these experiments are added proof that a stimulant is carried to the gastric glands through the blood stream.

## GASTRIC SECRETION

### II. STUDIES IN A TRANSPLANTED GASTRIC POUCH WITHOUT AUERBACH'S PLEXUS

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NEW YORK

In a previous paper<sup>1</sup> the mechanism of the gastric phase of secretion was discussed. Following the ingestion of certain food substances, such as meat, a humoral stimulant of gastric secretion appears in the blood stream. This stimulant is either a product of food digestion and is absorbed through the antrum or a hormone prepared by the antral cells and then liberated into the blood. At any rate it is the antrum, approximately the distal fifth of the stomach, which is involved in this mechanism. The humoral stimulant is then carried to the glands of the fundus, and there produces secretion. Neither the vagus nor the splanchnic nerves are necessary for this mechanism, for in a transplanted pouch made from the fundus of the stomach, the secretion still takes place.<sup>2</sup> In such a transplanted pouch there are two possible sites on which the stimulant may act: (1) the intrinsic gastric plexuses and (2) the gastric secretory cells themselves. In the present paper we shall discuss the results obtained from a transplanted gastric pouch that has been deprived of Auerbach's plexus.

#### THE RELATION OF THE EXTRINSIC NERVES TO AUERBACH'S PLEXUS

In the ordinary motor reflex, three nerve cells are involved: (1) the afferent nerve which terminates around a cell in the posterior horn, (2) a connector nerve which runs from this cell to a nerve cell in the anterior horn and (3) the nerve fiber which runs from the anterior horn to the muscle (fig. 1). In the case of the sympathetic nervous system (fig. 1), the afferent nerve runs, as described, in the posterior root into the cord. The second or connector nerve fiber does not pass to a cell within the spinal cord, but passes out through the anterior roots in the thoracolumbar portion of the spine to a number of ganglions situated on either

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From the Service of Dr. A. A. Berg and from the Department of Laboratories of the Mount Sinai Hospital.

1. Klein, Eugene, and Arnheim, Ernest: Gastric Secretion: I. Studies in a Transplanted Gastric Pouch with Auerbach's Plexus Removed, *Arch. Surg.*, this issue, p. 433.

2. Ivy, A. C., and Farrell, J. I.: Contributions to the Physiology of Gastric Secretion: VIII. The Proof of a Humoral Mechanism, *Am. J. Physiol.* **74**:639 1925. Klein and Arnheim (footnote 1).

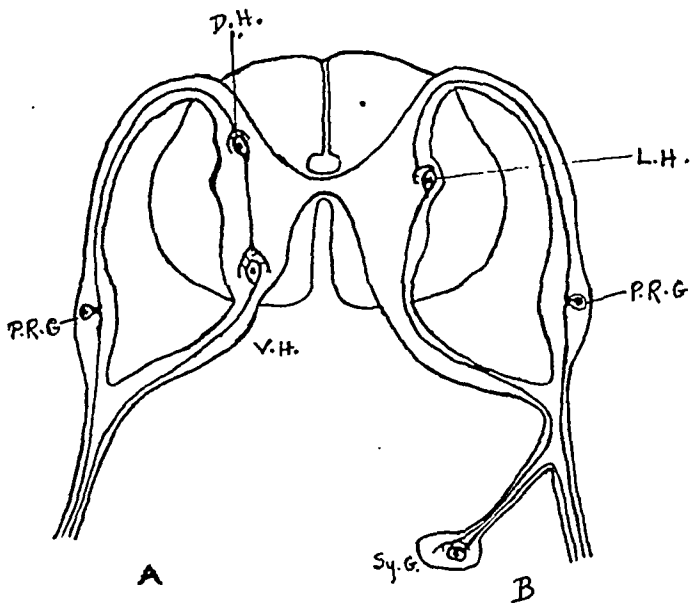


Fig. 1.—The reflex paths in the cord: *A*, those of the voluntary nervous system. The receptor neurons lie in the posterior root, their cells lying in the posterior root ganglion, *P. R. G.* The connector neurons lie in the dorsal horn, *D. H.*, the processes of which run in the anterior root. *B*, those of the involuntary nervous system. The receptor neurons run in the posterior root, their cells lying in the posterior root ganglion, *P. R. G.* The connector neurons lie in the lateral horn, *L. H.*, their processes running out in the anterior root and connecting, as the white ramus communicans, with the excitor neurons lying in the sympathetic ganglion, *Sy. G.* The processes of the excitor neurons form the gray ramus communicans, and run out in the spinal nerve (from Gaskell, W. H.: *The Involuntary Nervous System*, New York, Longmans, Green & Company, 1916).

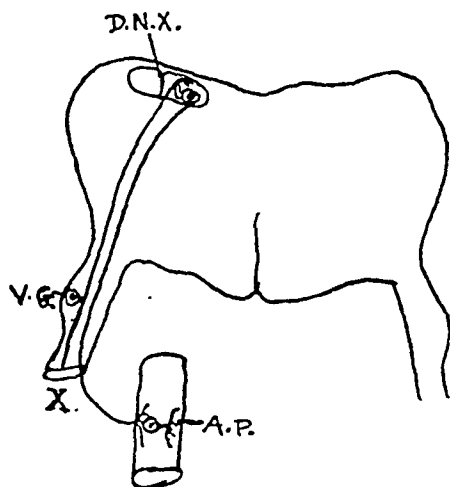


Fig. 2.—The reflex paths of the parasympathetic in the bulbar region. The receptor neurons run in the tenth nerve, *X*, with their cells in the ganglion of this nerve, *V. G.*, and connect with connector neurons that lie in the dorsal nucleus of the vagus, *D. N. X.* The processes of these connector neurons run out in the vagus nerve, *X*, and finally connect with the excitor neuron which lies on some peripheral organ, e. g., in the case of the stomach lying in Auerbach's plexus (from Gaskell, W. H.: *The Involuntary Nervous System*, New York, Longmans, Green & Company, 1916).



side of the vertebral column and on either side of the aorta. The third nerve fiber starts from cells in these ganglions and runs to the peripheral organ, such as the stomach. The latter fiber is known as the postganglionic. In the case of the parasympathetic nervous system (fig. 2), there is again first the primary afferent sensory stimuli. Then the vagus nerve carries the second or connector fibers to the cells of Auerbach's plexus. In this plexus, the third group of fibers arises from the ganglion cells, and the fibers pass to the tissues, which they innervate. In this case these are the postganglionic fibers. This plexus is situated between the inner and outer muscular coats of the stomach and intestine. Most of the fibers in it are derived from the vagus nerves, for if the vagi are sectioned and the plexus is examined after degeneration has taken place, the interlacing meshwork of fibers is nearly all gone, and only the local ganglion cells and their processes remain.<sup>3</sup>

#### PREPARATION OF THE SAC

It is possible to peel away both muscular coats from the submucosa. Since Auerbach's plexus, as has been stated, is situated between the circular and longitudinal muscle layers, it will be removed at the same time. Utilizing this fact, a pouch was prepared along the greater curvature. As the blood vessels enter along the greater curvature and pass almost directly to the submucosa, it is possible to do this without depriving the pouch of its blood supply. After the muscle was peeled away, the submucosa was further scraped with a scalpel to make sure that all muscular fibers had been removed. Sections were then taken both of the muscular coat and of the pouch wall consisting of the mucous membranes and submucosa to verify the fact that Auerbach's plexus had been removed (figs. 3 and 4). This pouch was placed in a prepared space in the subcutaneous tissues, its blood vessels reaching it through a small opening left in the peritoneum and fascia. After a period of from five to six weeks, these blood vessels to the pouch were severed through an abdominal incision. The final result then was a subcutaneous gastric pouch consisting of mucous membrane and submucosa completely cut off from the vagus and splanchnic nerves and with an entirely new blood supply from the abdominal wall. Unlike the other forms of gastric pouches, such a pouch does not empty itself, because the muscular coats have been removed and the muscularis mucosae does not possess sufficient contractile power to express the contents. Incidentally, it may be stated that following the peeling away of the outer muscular coats, the rugae disappear from the mucous membrane. This subject will be discussed in a subsequent paper.

#### METHODS

In the present paper the results in three dogs are reported. No food was allowed for twenty-four hours. A tube was then inserted into the sac, and the contents were carefully expressed. The tube was removed and reinserted the

3. Johnson, S. E.: *Experimental Degeneration of the Extrinsic Nerves of the Small Intestine in Relation to the Structure of the Myenteric Plexus*, *J. Comp. Neurol.* **38**:299, 1924-1925.

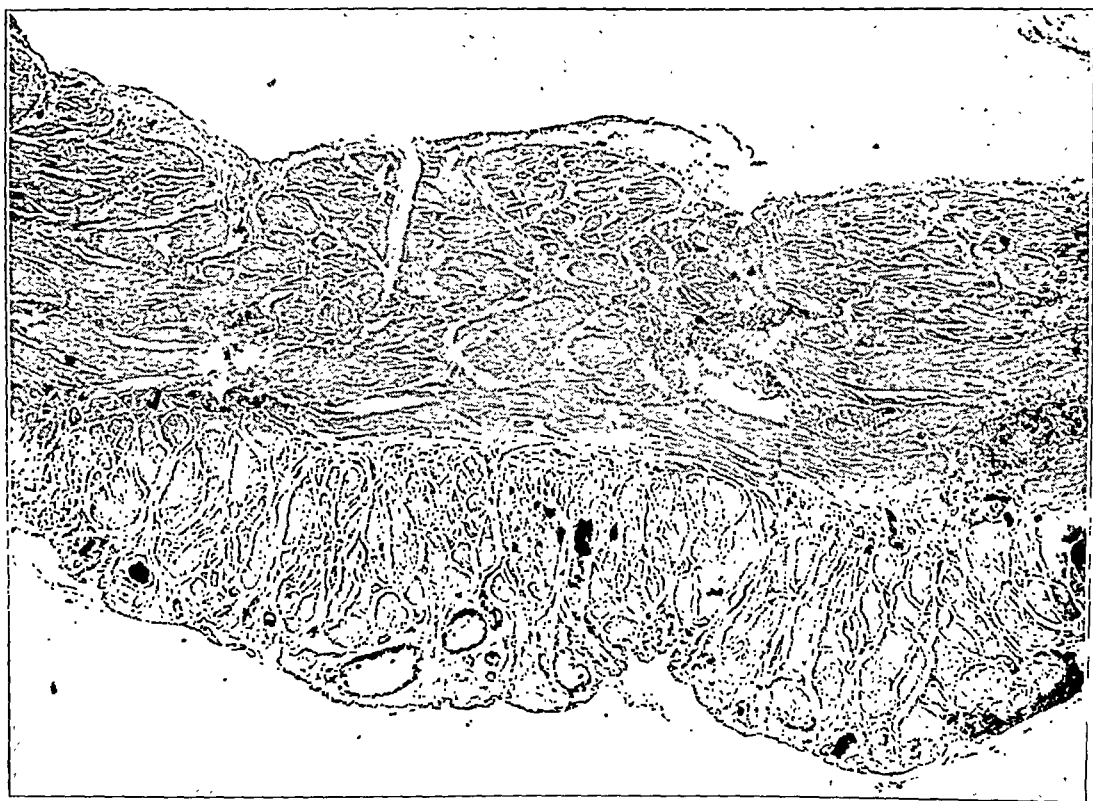


Fig. 3.—Circular and longitudinal muscle layers that have been peeled away from the inner coats shown in figure 4. Auerbach's plexus is situated between the two layers.

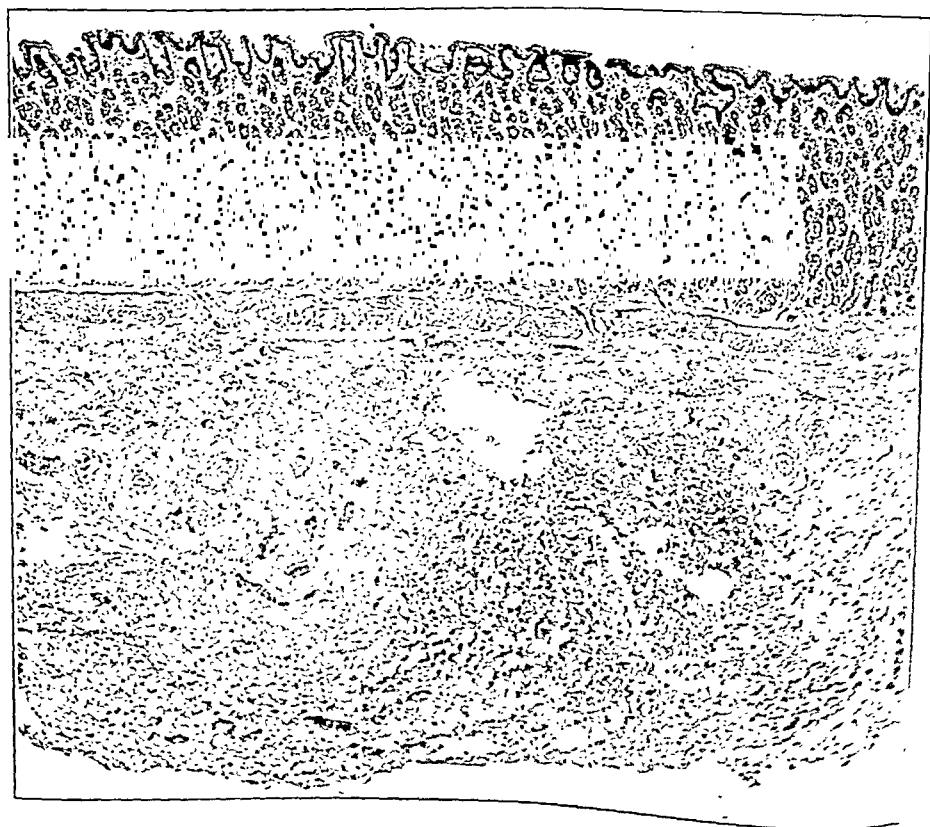


Fig. 4.—Wall of pouch, showing mucous membrane, muscularis mucosae and submucosa.

following hour, when the contents were again expressed. Since the sacs did not empty themselves during the hour, none of the fluid escaped. The dog was then fed 200 Gm. of meat and 150 cc. of water. The contents were collected each hour for the length of time shown in the tables. When tests for the presence of spontaneous secretion were desired, the procedure was carried out for several hours, except that no food was administered. Tests for acid were made by titrating the secretion with tenth-normal sodium hydroxide, using Toepfer reagent as indicator for free hydrochloric acid and phenolphthalein for total acid. The results are expressed in the usual manner, namely, the number of cubic centimeters of tenth-normal sodium hydroxide neutralized by 100 cc. of the gastric juice.

To bring all figures to a common denominator, total chlorides have been expressed in the same way, that is, as cubic centimeters of tenth-normal solution. To convert total chloride figures to milligrams of chlorine per hundred cubic centimeters, multiply them by 0.00355. To convert free hydrochloric acid to milligrams of hydrochloric acid for 100 cc., multiply by 0.00365.

TABLE 1.—*Dog 84, with Transplanted Gastric Pouch Without Auerbach's Plexus, Before Gastric Blood Vessels Were Divided. Fed at the Beginning of the First Hour (for Description of Methods See Text)*

Hour	Volume of Juice, Cc.	Free Hydrochloric Acid	Total Hydrochloric Acid	Total Chloride	Pepsin, Mett	Volume of Mucus, %
1	4.0	30	50	128	256	0
2	4.3	55	75	136	576	0
3	6.7	75	90	140	576	0
4	7.3	80	95	140	576	0

The presence of pepsin was determined by Mett tubes. One cubic centimeter of the pouch secretion was diluted sixteen times with twentieth-normal hydrochloric acid. The number of millimeters digested was squared and multiplied by 16.

Mucus is described as a trace or as the relative volume of mucus to the total volume of secretion in each sample collected.

#### EXPERIMENTAL WORK

PROTOCOL 1.—Dog 84, female, had the first operation performed on Jan. 13, 1931. This consisted in the preparation of the sac and its implantation into the subcutaneous tissues. The blood supply was left intact. The results of the first test done on January 21 are given in table 1. It is probable, of course, that some sympathetic nerves still reached the pouch along the blood vessels in the submucosa. The results do not differ much from those in the ordinary Haidenhain pouch.

On February 17, the blood vessels to the pouch were severed. Tables 2 and 3 show the tests done following this procedure. There was a drop in the quantity of secretion, the free hydrochloric acid disappeared, the total hydrochloric acid was reduced, and the pepsin was moderately reduced. The total chloride secretion remained practically unchanged. There was a marked increase in the amount of mucus secreted.

For about a month all tests showed similar results. Then there was a gradual reappearance of hydrochloric acid. Five weeks after the test shown in table 3, there was a good response of free hydrochloric acid to the test meal, as shown in table 4. The quantity of secretion was increased. The free acid was quite high.

TABLE 2.—*Dog 84, Four Weeks After Severing Gastric Blood Vessels.  
Fed at Beginning of First Hour*

Hour	Volume of Juice, Cc.	Free Hydrochloric Acid	Total Hydrochloric Acid	Total Chloride	Mucus
1	1.5	0	40	160	Heavy trace
2	0.7	0	60	142	Heavy trace
3	0.15	0	50	...	Heavy trace
4	0.42	0	80	...	Heavy trace
5	0.35	0	70	...	Heavy trace

TABLE 3.—*Dog 84, Five Weeks After Severing Gastric Blood Vessels.  
Fed at Beginning of First Hour*

Hour	Volume of Juice, Cc.	Free Hydrochloric Acid	Total Hydrochloric Acid	Total Chloride	Pepsin, Mett	Volume of Mucus, %
1	2.9	0	35	142	256	50
2	1.9	0	55	134	256	25
3	0.8	0	55	130	...	100
4	1.0	0	40	126	...	100
5	0.9	0	45	130	...	100

TABLE 4.—*Dog 84, Ten Weeks After Severing Gastric Blood Vessels. Fed at Beginning of First Hour*

Hour	Volume of Juice, Cc.	Free Hydrochloric Acid	Total Hydrochloric Acid	Total Chloride	Pepsin, Mett	Volume of Mucus, %
1	2.2	55	75	148	288	Trace
2	3.5	79	95	152	448	0
3	3.8	75	100	152	400	5
4	5.5	70	95	156	256	Heavy trace
5	2.5	85	110	160	288	Trace
6	2.2	90	110	156	400	10
7	2.0	75	105	152	256	0
8	1.5	90	110	156	...	20

Mucus was diminished in quantity. The secretion of pepsin was increased. The total chlorides were slightly increased.

Table 5 shows the results of a test for spontaneous secretion. Neither food nor any other stimulus was administered. Under such conditions, secretions could nearly always be obtained in this dog. Free hydrochloric acid was present only once in such a test, table 6, but total acid was always present. There was invariably a large amount of mucus. Pepsin was always present in every sample examined. The total chlorides were within the same limits as after stimulation by food.

Table 7 shows a test performed four and one-half months after the blood vessels of the sac were severed. It still responds readily to food stimulation.

To summarize, the important findings following the severance of the blood supply to the sac were: (1) a drop in secretion and disappearance of free acid;

TABLE 5.—*Dog 84, Ten Weeks After Severing Gastric Blood Vessels. Spontaneous Secretion*

Hour	Volume of Juice, Cc.	Free Hydrochloric Acid	Total Hydrochloric Acid	Total Chloride	Pepsin, Mett	Volume of Mucus, %
1	1.9	0	15	142	...	100
2	1.0	0	20	148	...	100
3	2.3	0	10	154	288	100
4	2.8	0	20	158	256	100
5	2.7	0	25	148	400	100
6	1.5	0	15	152	...	100

TABLE 6.—*Dog 84, Three Months After Severing Gastric Blood Vessels. Spontaneous Secretion*

Hour	Volume of Juice, Cc.	Free Hydrochloric Acid	Total Hydrochloric Acid	Total Chloride	Pepsin, Mett	Volume of Mucus, %
1	1.1	4	52	142	144	33
2	1.3	0	28			33
3	1.2	4	58			100
4	0.9	0	36	...	...	100
5	0.7	8	44	...	...	100
6	0.9	12	52	...	...	100

TABLE 7.—*Dog 84, Four and One-Half Months After Severing Gastric Blood Vessels. Fed at End of First Hour*

Hour	Volume of Juice, Cc.	Free Hydrochloric Acid	Total Hydrochloric Acid	Total Chloride	Pepsin, Mett	Volume of Mucus, %
1	0.3	10	40	...	...	Trace
Fed 200 Gm. of meat and 150 cc. of water						
2	2.5	60	90	152	96	20
3	2.8	55	90	150	122	Trace
4	2.2	35	75	146	192	10
5	0.7	10	50	...	171	100
6	0.5	0	30	...		100

TABLE 8.—*Dog 90, with Transplanted Gastric Pouch Without Auerbach's Plexus, Seven Days After Preparation of Pouch and Before Gastric Blood Vessels Were Divided. Fed at Beginning of First Hour*

Hour	Volume of Juice, Cc.	Free Hydrochloric Acid	Total Hydrochloric Acid	Total Chloride	Pepsin, Mett	Volume of Mucus, %
1	9.5	90	105	160	614	Trace
2	8.4	100	113	164	576	Trace
3	6.5	90	120	166	576	5
4	4.2	70	100	160	448	10
5	5.8	55	110	156	400	5

(2) a gradual increase in the secretory response to food with the reappearance of free acid at the end of one month and a good response four months after the sac was prepared; (3) the presence of pepsin in all samples examined, even in the absence of free hydrochloric acid; (4) the presence of a continuous secretion usually containing no free hydrochloric acid, but always containing combined acid

and pepsin, and (5) the total chlorides, whether free acid was present or not and whether the secretion was in response to food or not, varied within fairly narrow limits. For the most part, they were between 138 and 152 tenth-normal hydrochloric acid.

PROTOCOL 2.—Dog 90, female, had the first operation performed on March 27, 1931. The first test is shown in table 8. One week later the secretion dropped

TABLE 9.—*Dog 90, Fourteen Days After Preparation of Pouch and Before Gastric Blood Vessels Were Divided. Fed at End of First Hour*

Hour	Volume of Juice, Cc.	Free Hydrochloric Acid	Total Hydrochloric Acid	Total Chloride	Pepsin, Mett	Volume of Mucus, %
1	2.5	30	38	...	...	33
Fed 200 Gm. of meat and 150 cc. of water						
2	5.2	88	92	...	...	10
3	2.7	96	108	...	...	10
4	3.0	102	110	...	...	Trace
5	1.9	100	108	...	...	Trace
6	2.2	108	116	...	...	Trace

TABLE 10.—*Dog 90, One Week After Severing Gastric Blood Vessels. Fed at End of First Hour*

Hour	Volume of Juice, Cc.	Free Hydrochloric Acid	Total Hydrochloric Acid	Total Chloride	Pepsin, Mett	Volume of Mucus, %
1	1.1	0				
Fed 150 Gm. of meat and 150 cc. of water						
2	1.3	75	120	...	...	Trace
3	0.8	60	115	...	...	100
4	1.2	50	100	...	...	50
5	0.9	55	115	...	...	50
6	0.6	70	125	...	...	100

TABLE 11.—*Dog 90, Two and One-Half Months After Severing Gastric Blood Vessels. Fed at End of First Hour*

Hour	Volume of Juice, Cc.	Free Hydrochloric Acid	Total Hydrochloric Acid	Pepsin, Mett	Volume of Mucus, %
1	0.1	0	..	..	100
Fed 200 Gm. of meat and 150 cc. of water					
2	0.5	50	80	84	100
3	0.3	40	65		100
4	0.25	45	70		100
5	0.5	40	60		66
6	0.45	30	45	46	100
7	0.1	+	..		100
8	0.3	20	40		100
9	0.4	15	30		100
10	0.55	..	30		100

markedly, as shown in table 9. The blood vessels to the pouch were severed on April 13. The first test was made one week after this procedure, and the results are shown in table 10. Here again there is a decided drop in the secretion, relatively more marked in the volume than in the free and total acid. There followed a gradual drop in the secretion, so that on June 30, the results were as shown in table 11.

Spontaneous secretion was irregularly present. It was usually small in quantity, but often not less than after the administration of meat. But free hydrochloric

acid was present only once, the amount of total acid was low, and mucus was present in large amounts. The results of a typical test are shown in table 12.

If these findings are summarized the results are: (1) an initial hypersecretion after preparation of the sac; (2) a drop in secretion after severing the blood vessels to the sac; (3) a spontaneous secretion not constantly present, small in quantity, rich in mucus, only once containing free acid and with a very low figure for total acid (on one occasion, however, the total acid reached 75); (4) the presence of pepsin, and (5) definite secretory response to a food stimulus gradually diminishing and then persisting at a low level.

TABLE 12.—*Dog 90, One and One-Half Months After Severing Gastric Blood Vessels. Spontaneous Secretion*

Hour	Volume of Juice, Cc.	Free Hydrochloric Acid	Total Hydrochloric Acid	Volume of Mucus, %
1	0.0	0	..	100
2	0.1	0	..	100
3	0.15	0	40	100
4	0.2	0	30	100
5	0.4	0	40	100
6	0.5	0	30	100

TABLE 13.—*Dog 88, with Transplanted Gastric Pouch Without Auerbach's Plexus, Three Weeks After Preparation of Sac. Gastric Blood Vessels Not Divided. Fed at Beginning of First Hour*

Hour	Volume of Juice, Cc.	Free Hydrochloric Acid	Total Hydrochloric Acid	Total Chloride	Volume of Mucus, %
1	1.4	38	62	162	20
2	1.3	36	58	162	20
3	1.2	36	60	156	20
4	1.3	42	68	156	25
5	1.7	26	48	160	20

TABLE 14.—*Dog 88, Four Weeks After Preparation of Sac. Gastric Blood Vessels Not Divided. Fed at Beginning of First Hour*

Hour	Volume of Juice, Cc.	Free Hydrochloric Acid	Total Hydrochloric Acid	Total Chloride	Pepsin, Mett	Volume of Mucus, %
1	3.9	55	95	148	288	20
2	2.8	60	100	156	400	25
3	0.7	30	70	156	256	50
4	0.9	25	60	148	144	50
5	0.7	30	55	...	256	100

PROTOCOL 3.—Dog 88, male, had the first stage operation performed on Feb. 26, 1931. In this dog, the blood vessels, that is, the original vasa brevia, were not subsequently severed. We therefore had a pouch without the vagi and without Auerbach's plexus. It is possible that some of the sympathetic nerves passed with the vessels of the submucosa to the sac.

Tables 13 and 14 show the findings on March 17 and on March 25. The results remained practically the same for about two months, and then there was a gradual increase in the amount of the secretion as shown in table 15. But the amounts varied, as is shown in table 16.

The total chlorides remained constant. Pepsin was present in all samples examined, but the later tests showed gradually diminishing concentration in spite

of the increasing volume of secretion already mentioned. The pepsin concentration did not seem to be higher than in the other dogs in which the gastric blood vessels were severed.

Spontaneous secretion was not present constantly, and when present was always scant (table 17), but free hydrochloric acid was occasionally present and at times was quite high, reaching a figure of 85.

TABLE 15.—*Dog 88, Four Months After Preparation of Sac. Gastric Blood Vessels Not Divided. Fed at the End of the First Hour*

Hour	Volume of Juice, Cc.	Free Hydrochloric Acid	Total Hydrochloric Acid	Total Chloride	Pepsin, Mett	Volume of Mucus, %
1	0.4	20	50	...	..	100
Fed 200 Gm. of meat and 150 cc. of water						
2	6.1	75	110	152	25	Trace
3	3.4	70	100	154	36	Trace
4	2.2	55	85	142	26	20
5	1.7	50	90	146	40	20
6	2.2	60	95	144	36	33

TABLE 16.—*Dog 88, Four and One-Half Months After Preparation of Sac. Gastric Blood Vessels Not Divided. Fed at the End of the First Hour*

Hour	Volume of Juice, Cc.	Free Hydrochloric Acid	Total Hydrochloric Acid	Total Chloride	Pepsin, Mett	Volume of Mucus, %
1	0.9	10	35	...	..	Trace
Fed 200 Gm. of meat and 150 cc. of water						
2	1.6	70	100	...	64	Trace
3	2.2	50	80	142	82	Trace
4	0.6	40	60	142	..	Trace
5	1.3	10	45	...	64	33
6	0.5	10	40	...	..	100
7	0.4	5	30	140	..	100
8	0.15	0	15	...	..	100
9	0.15	5	20	...	..	100
10	0.9	15	45	...	..	100

TABLE 17.—*Dog 88, One and One-Half Months After Preparation of Sac. Gastric Blood Vessels Not Divided. Spontaneous Secretion*

Hour	Volume of Juice, Cc.	Free Hydrochloric Acid	Total Hydrochloric Acid	Volume of Mucus, %
1	0.5	65	78	Trace
2	0.1	0	..	100
3	0.1	0	..	100
4	0.0	—	..	100
5	0.1	0	..	100
6	0.0	—	..	100

The results of these tests showed:

1. There was a response to food stimulus which slowly became more marked.
2. Total chlorides in all cases remained within narrow limits.
3. Pepsin was always present in any secretion, although in the later tests the concentration was relatively low and never higher than in the pouches in which the vasa brevia were divided.
4. A spontaneous secretion was irregularly present but usually scant, although the acid values in it were often quite high.



## COMMENT

1. *Secretion in Response to Food.*—Following the ingestion of meat and water, all of the pouches showed secretion of hydrochloric acid and pepsin from the pouch. In view of the fact that both the vagus and the plexus of Auerbach had been eliminated, it can definitely be said that a humoral stimulus for secretion may act in the absence of the preganglionic and postganglionic fibers of Auerbach's plexus. It is true that Meissner's plexus was still left in these pouches, but much confusion exists concerning this plexus. It has been ascribed to the sympathetic system<sup>4</sup> and is bound up with the tonus of the muscularis mucosae.<sup>5</sup> It therefore appears that the humoral stimulant acts directly on the secretory cells themselves or on the neurocellular substance. Tests with pilocarpine, a drug that stimulates the vagus system, are being done and will later be reported.

2. *The Spontaneous Secretion.*—In dog 84, there was a spontaneous secretion which could be obtained almost constantly, and which contained fairly marked concentration of free hydrochloric acid. Pepsin was also present at all times. The quantity of the secretion was often as large as that obtained after food stimulation, but the acid concentration was lower. In dogs 90 and 88 a spontaneous secretion was present only at times and only occasionally contained free acid, but the free acid could reach high levels.

The question as to whether there is spontaneous gastric secretion has long been troublesome. On the one hand, were Pavlov's findings that there is no secretion without stimulation. On the other, was the undoubted presence of secretion in the stomach of man during long interdigestive phases. Secretion in the latter case and similar types of secretion in animals may be explained in large measure as cephalic in character and due to conditioned reflexes.<sup>6</sup> The thought of food and its association with certain fixed times and places are enough to cause secretion. This secretion is of course transmitted through the vagus nerves. But it has also been known that in a Heidenhain<sup>7</sup> pouch a continuous secretion may persist for a long time.<sup>8</sup> In this type of pouch

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4. Langley, in Shaefer: Textbook of Physiology, New York, The Macmillan Company, 1900, vol. 2, p. 616.

5. King, C. E., and Arnold, Lloyd: The Activities of the Intestinal Mucosal Motor Mechanism, Am. J. Physiol. 59:97, 1922.

6. Babkin, B. P.: Die Äussere Sekretion der Verdauungsdrüsen, Berlin, Julius Springer, 1928, p. 191.

7. A Heidenhain pouch is made from a portion of the stomach that has been cut away along the greater curvature. The blood vessels attached to the part are left intact. The pouch is left in the abdominal cavity and communicates with the exterior through a fistula.

8. Babkin (footnote 6, p. 357).

nearly all of the vagus nerves are sectioned, although a few may reach the pouch by running through the omentum.

The secretion has been explained by the assumption that a humoral stimulus is present practically constantly in the blood stream. Bickel,<sup>9</sup> for instance, made use of that hypothesis, and assumed that this stimulant is ordinarily inhibited by certain fibers in the vagi. Krimberg<sup>10</sup> also assumed the formation of a gastric secretin in the bodily tissues. There is a further possible explanation in the fact that saliva and pancreatic secretion are known to be stimulants of the humoral or secondary phase of gastric secretion. They exert this influence from the stomach. However, if these hypotheses are true, it is not clear why a more marked secretion was not present in dogs 90 and 88. It may be that some unknown technical factor in the construction of the pouch interfered. That secretion is present cannot, however, he gainsaid, nor could it have been due to a conditioned reflex acting on the sac, as no nerves reached it. Apparently, the secretion originated in the cells themselves or was the result of a stimulus transmitted through the blood.

3. *Initial Hypersecretion.*—This phenomenon has been noted before and may occur after operative procedures in the stomach, especially those injuring secretory nerves. It has been reported also as occurring after the preparation of Heidenhain pouches.<sup>11</sup>

4. *Drop in the Secretion After Section of Blood Vessels to the Pouch.*—The second stage of the operation consisted, as has been stated, in dividing the gastric vessels, which had been left attached to the pouch until a new circulation in the abdominal wall had been established. After this procedure there was a drop in the volume and acidity of the secretion. This can be seen in the results obtained for dogs 84 and 90. The drop in volume is more striking than the drop in the acidity. The same phenomenon was noted by Ivy and Farrell<sup>12</sup> in pouches transplanted into the mammary gland and in the pouches previously reported.<sup>13</sup> These pouches consisted of the entire gastric wall. The drop in pepsin is also not very marked. The drop in secretion may be due to division of the blood vessels, to division of the sympathetic nerves accompanying them or to both. Some observers feel that the sympathetic nerve may be responsible for part of the gastric secretion. Bickel<sup>9</sup> thinks that pepsin secretion is

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9. Bickel, A.: Die nervöse Mechanismus der Sekretion der Magendr sen und der Muskelbewegung am Magendarm kanal, *Ergebn. d. Physiol.* **24**:228, 1925.

10. Krimberg, R.: Zur Frage nach der Bedeutung der Muskelhormone im Sekretionsprozessen der Verdauungsdr sen, *Biochem. Ztschr.* **157**:187, 1925.

11. Babkin (footnote 8).

12. Ivy and Farrell (footnote 2, first reference).

13. Klein and Arnheim (footnote 1).

stimulated by the sympathetic, and Volborth and Kudryavzeff<sup>14</sup> reported secretion in the whole stomach and in Heidenhain pouches after sympathetic stimulation by electricity. But most observers believe that the sympathetics are little if at all involved in the stimulation of fluid and hydrochloric acid secretion. Thus it seems most likely that the sudden diminution in the blood supply after severance of the vessels is responsible for the drop. Obviously, less blood reaches the pouch through new blood vessels from the subcutaneous tissues than through the original blood vessels supplying the pouch. Less blood means less of the factors necessary for the production of secretion, and it also means less secretin or hormone. One striking fact stands out, however; namely, the total chlorides remain practically unchanged.

5. *Gradual Increase in Secretion.*—In dogs 84 and 90, an increase in the secretion, both in the amount and in the percentage, of free hydrochloric acid was noted after several months. It seems possible that the condition is the reverse of the one just discussed. With the establishment of a better blood supply to the pouch, more secretion resulted.

6. *Constancy of Total Chloride Secretion.*—The whole subject of the secretion of chlorides will be discussed in a subsequent paper. Attention, however, is drawn to the fact that the concentration of the total chlorides is fairly constant, regardless of whether the secretion contains a large amount of hydrochloric acid or none at all, and the actual amount of chlorine is quite high, for if it were all present as free hydrochloric acid, it would reach a figure of from 140 to 150 tenth-normal hydrochloric acid. It is further interesting to note that the relative value of the chlorides in the blood is about from 90 to 95 cc. tenth-normal.<sup>15</sup>

7. *The Pepsin Secretion.*—Pepsin was present in all of the samples. As previously described, Mett tubes were used to determine the relative quantities. This method is hardly an accurate one from the quantitative standpoint, but it does show the presence or absence of the ferment and gives some knowledge of the relative quantities.

In dog 84, the concentration per cubic centimeter of pepsin after the severance of the blood vessels remained about the same. The total quantity, of course, dropped, because the quantity of secretion dropped. There followed next a gradual drop in the concentration of the pepsin over a period of months, but some pepsin was always present. In dog

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14. Volborth, G. W., and Kudryavzeff, N. N., quoted by Babkin (footnote 6, p. 326); *The Splanchnic Nerve as a Secretory Nerve of the Gastric Glands*, Am. J. Physiol. **81**:154, 1927.

15. Expressed in milligrams of sodium chloride, the blood contains about 540 mg. per hundred cubic centimeters, whereas the gastric juice referred to would contain from 800 to 900 mg. per hundred cubic centimeters.

88, the drop was also noted, although the blood vessels had not been severed. In dog 90, the quantities of secretion after severance of the blood vessels were usually too small to make determinations, but whenever the tests were made, they confirmed these results.

TABLE 18.—*Histamine Secretion. Dog 84, Three and One-Half Months After Severing Gastric Blood Vessels. One Cubic Centimeter of Histamine Injected Subcutaneously at End of First Hour. First Secretion Obtained Fifteen Minutes After the Injection*

Hour	Volume of Juice, Cc.	Free Hydrochloric Acid	Total Hydrochloric Acid	Total Chloride	Pepsin, Mett	Volume of Mucus, %
1	2.6	0	70	146	64	50
1 cc. of histamine injected subcutaneously						
2	7.3	75	105	151	36	Trace
3	3.2	30	90	150	25	16
4	1.0	0	70	144	..	100
5	1.2	0	65	146	..	100
6	0.8	0	55	144	..	100

TABLE 19.—*Histamine Secretion. Dog 90, Six Weeks After Severing Gastric Blood Vessels. One Cubic Centimeter of Histamine Injected Subcutaneously at End of First Hour \**

Hour	Volume of Juice, Cc.	Free Hydrochloric Acid	Total Hydrochloric Acid	Total Chloride	Volume of Mucus, %
1	0.8	0	40	144	Trace
1 cc. of histamine injected subcutaneously					
2	2.7	50	85	150	Trace
3	0.7	40	65	146	Trace
4	0.0				
5	0.0				

\* In a second test in which there was no secretion during the first control hour, the latent period following the injection of the histamine was fifteen minutes.

TABLE 20.—*Histamine Secretion. Dog 88, Three and One-Half Months After Preparation of Sac. Original Blood Supply Left Intact. One Cubic Centimeter of Histamine Injected Subcutaneously at End of First Hour. First Secretion Obtained Twelve Minutes After the Injection*

Hour	Volume of Juice, Cc.	Free Hydrochloric Acid	Total Hydrochloric Acid	Total Chloride	Pepsin, Mett	Volume of Mucus, %
1	0.2	0	55	...	...	100
1 cc. of histamine injected subcutaneously						
2	3.5	45	70	144	144	Trace
3	0.4	10	60	...	...	Trace
4	0.0					

In the spontaneous secretion of dog 84 and dog 88, whenever the quantities were sufficient to permit examination for pepsin, the presence of the ferment could be demonstrated. It did not vary much from the amounts found in tests done about the same time following the administration of meat. This question will be further discussed when the secretion of histamine is considered.

8. *Effect of Histamine.*—All of the pouches responded to the subcutaneous injection of 1 mg. of histamine (tables 18, 19 and 20). The latent period was usually from twelve to fifteen minutes, which is almost normal. There was an increase in the quantity of the secretion and in free acid. The effect was usually over in two hours, though it occasionally persisted two or three hours more in dog 84. Pepsin was found in all of the specimens examined. It did not vary much in quantity from the amounts found after food stimulation or in the spontaneous secretion obtained in tests done about the same time.

Vineberg and Babkin<sup>16</sup> recently called attention to the fact that histamine chiefly stimulates the secretion of fluid and hydrochloric acid, and that it has little or no effect on the secretion of pepsin. The latter they believe due to vagus stimuli, and they have produced it with pilocarpine, which stimulates this system. Gilman and Cowgill<sup>17</sup> have reported similar results with histamine studies. The results reported in tables 18, 19 and 20 also show that histamine does not increase the secretion of pepsin. On the other hand, it is definitely established in these pouches that fair quantities of pepsin can be secreted over periods of hours in spite of the entire absence of the vagi and of the plexus of Auerbach.

The stimulus for the secretion of pepsin in these pouches is not clear. It may be due to some property of the peptic cell or to a humoral stimulus, although the latter does not seem likely.

These pouches furnish excellent means for further study concerning the effect of pilocarpine, histamine and atropine on gastric secretion.

#### SUMMARY

1. A transplanted gastric pouch was prepared from the mucous membrane and submucosa.

2. Auerbach's plexus was eliminated from this pouch in addition to the vagus and sympathetic nerves and the normal gastric blood supply.

3. This pouch responded to food with the secretion of gastric juice containing hydrochloric acid and pepsin, showing that this secretion may take place in the entire absence of the preganglionic and postganglionic fibers of Auerbach's plexus.

4. The stimuli for this secretion apparently reach the sac through the new abdominal blood supply and act on the secreting cells themselves or on the neurocellular substance.

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16. Vineberg, A. M., and Babkin, B. P.: Histamine and Pilocarpine in Relation to Gastric Secretion, *Am. J. Physiol.* **97**:69, 1931.

17. Gilman, A., and Cowgill, G. R.: Effect of Histamine on Secretion of Gastric Pepsin, *Am. J. Physiol.* **97**:124, 1931.

5. A fairly marked spontaneous secretion containing free hydrochloric acid and pepsin was present in one dog. In the other two, it was irregularly found and usually scanty. The origin of this secretion is not clear. Some possible causes are discussed.

6. The amount of the blood supply to the sac seems to determine in part the amount and the nature of the secretion. After the second stage of the operation, which consisted in dividing the gastric vessels, there was a drop in the quantity of the secretion and in the hydrochloric acid. Later there was a rise in one dog probably owing to the development of a better blood supply from the abdominal wall.

7. The quantities of the total chlorides remained fairly constant, between 140 and 150 cc. of tenth-normal solution (from 800 to 900 mg. of sodium chloride per hundred cubic centimeters), regardless of the conditions under which the secretion was collected.

8. Pepsin was always present, showing that at least a basic pepsin secretion could take place in the absence of the vagi and Auerbach's plexus.

9. The pouches responded to the stimulation of histamine after a latent period of from twelve to fifteen minutes. Pepsin was found in the secretion.

# SQUAMOUS CELL CARCINOMA OF THE RENAL PELVIS ASSOCIATED WITH STONE AND LEUKOPLAKIA

W. J. POTTS, M.D.

OAK PARK, ILL.

The following case is reported because it represents from a clinical and pathologic standpoint the various stages in the development of a squamous cell carcinoma of the renal pelvis. Reports of similar cases, although not frequent, illustrate the important relation of irritation<sup>1</sup> to leukoplakia, and of continued irritation to consequent carcinomatous changes.

Kutmann<sup>1a</sup> reported a case of leukoplakia in the renal pelvis, and stated that only 67 similar unquestioned cases had been reported. Patch<sup>2</sup> found reports of 152 cases of squamous cell carcinoma in the urinary tract; 36 renal, 6 ureteral and 10 vesical. In 13 cases, cancer and leukoplakia coexisted.

Equally interesting is the relation of calculi to the development of squamous cell tumors. Wells<sup>3</sup> in 1922 found reports of 11 unquestioned cases of squamous cell cancer of the renal pelvis, and reported a case of his own. The presence of calculi was mentioned in 6 reports. Scholl and Foulds<sup>4</sup> in 1924 reported 5 similar cases that had been observed at the Mayo Clinic between 1907 and 1922. Four of these were associated with stone. In cancer of the gallbladder, likewise, calculi are an important etiologic factor. Nicholson<sup>5</sup> reported 16 cases

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From the Senkenberg Pathological Institute, Frankfort-on-the-Main, Germany (Prof. B. Fischer-Wasels, director).

1. In this connection, the excellent work of Professor Fischer-Wasels should be referred to. He expressed the belief that chronic inflammation stimulates the regenerative processes that eventually develop into carcinomatous changes (Wien. klin. Wchnschr. **44**:629, 1931; München. med. Wchnschr. **75**:73, 1928; Klin. Wchnschr. **6**:1025, 1927).

1a. Kutzmann, A. A.: Leukoplakia of the Renal Pelvis, Arch. Surg. **19**:871 (Nov.) 1929.

2. Patch, F. S.: The Association Between Leukoplakia and Squamous Cell Carcinoma in the Upper Urinary Tract, New England J. Med. **200**:423, 1929.

3. Wells, H. G.: Chemical Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1925, p. 306; Primary Squamous Cell Carcinoma of the Kidney Pelvis as a Sequel to Renal Calculi, Arch. Surg. **5**:356 (Sept.) 1922.

4. Scholl, A. J., and Foulds, G.: Squamous Cell Tumors of the Renal Pelvis, Ann. Surg. **80**:594, 1924.

5. Nicholson, G. W.: Three Cases of Squamous Cell Carcinoma of the Gall-Bladder, J. Path. & Bact. **13**:41, 1909.

of squamous cell cancer in the bile tract, 15 of which were associated with cholelithiasis. Chiari<sup>6</sup> stated that in the postmortem material of the Allgemeines Krankenhaus in Vienna, cancer of the gallbladder is invariably associated with cholelithiasis or cholecystitis or with both. He further stated that carcinomatous changes are found at post-mortem examination in 18 per cent of cases with chronic cholelithiasis.

The relation of chronic irritation by calculi to the development of cancer must by force of repeated observation be accepted as a fact.

#### REPORT OF A CASE

*History.*—Mrs. W., aged 67, entered the Staedisches Krankenhaus, Frankfurt-on-the-Main, on Nov. 3, 1926, complaining of increasingly severe pain in the right flank, which was made worse by coughing or straining. During the previous few months, the patient had complained of pain in the bladder and urgency and frequency of urination. Before that she had been bothered with attacks of gall-stone colic, which in the latter years subsided spontaneously. In general, she had been well, the mother of five normal children.

*Clinical Examination.*—Physical examination revealed an old, well preserved woman, not acutely ill. The skin and the mucous membranes were normally pink; the tongue was clean, but somewhat dry. The only other positive physical finding was in the right upper quadrant of the abdomen, where a tender mass, presumably the kidney, could be felt. It moved with each deep respiration and could be moved by palpating bimanually.

An analysis of the contents of the stomach showed free acid 2 and combined acid 18. The blood pressure was 120 systolic and 70 diastolic. The hemoglobin was 77; the leukocyte count, 7,500; the Wassermann reaction, negative. Roentgen examination of the stomach and colon showed nothing abnormal. Urinalysis revealed albumin ++, pus cells ++++ and sugar 0.

Cystoscopic examination revealed a severe cystitis. Cloudy, flocculent urine was seen flowing from the right ureteral opening. Pyelograms of the left side showed no abnormality of the renal pelvis or of the ureter. In the roentgenograms of the right side, a shadow approximately 2 cm. in diameter was visible.

*Clinical Diagnosis.*—The clinical diagnosis was stone in the right kidney with pyelitis.

*Operation.*—On March 13, 1926, with the patient under ether anesthesia, the kidney was exposed by the usual curved flank incision and resection of the twelfth rib. The stone was easily identified high in the pelvis under a markedly thinned out area of renal tissue. A small incision was made through the parenchyma and the stone removed. A large amount of purulent fluid escaped. A rubber tube drain and catheter tied together were inserted into the kidney. The muscle wound was not sewed, but packed with a large gauze tampon. The stone was the size and shape of a horse chestnut. Chemical analysis showed it to be of calcium composition.

*Postoperative Course.*—The convalescence was smooth. The temperature remained normal. Daily lavage of the renal pelvis with a flavine dye in salt solution was practiced. The flank wound healed slowly, but the fistula, from

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6. Chiari: Personal communication.



which cloudy urine continued to escape, did not close over a period of four months in the hospital. Because of the patient's age it was decided to forego any further operation, and she was discharged.

She returned to the Surgical Clinic on Jan. 22, 1931, in a semicomatose, cachectic condition, and died three days later. During the intervening five years, the fistula had remained open and had drained pus and urine.

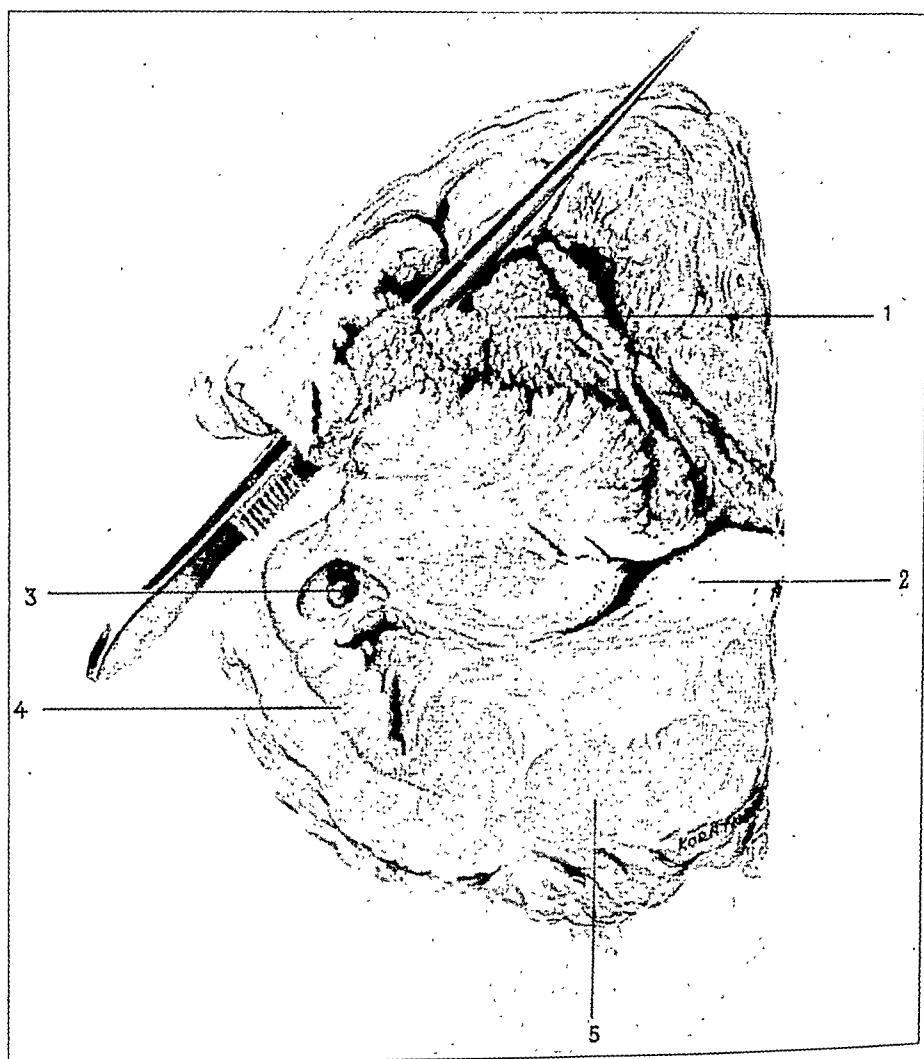


Fig. 1.—Gross appearance of one half of the tumor. The forceps is inserted through the fistula. The numerals indicate (1) tumor tissue, (2) leukoplakia, (3) stone in calix, (4) remnant of renal tissue and (5) fat.

*Postmortem Examination.*—The body was that of an old woman in poor general condition, 151 cm. long and weighing 41 Kg. In the right flank there was a healed renal incision, in the middle of which was a fistula 1 cm. in diameter, from which flocculent, turbid fluid escaped.

The peritoneum was smooth and shiny. The bowels were free, the mesenteric lymph glands not large. In the region of the right kidney, a mass could be felt, which was firmly fixed in the surrounding tissue. The left kidney was freely movable.

At the bases of both lungs were dense fibrous adhesions. The pericardial surfaces were smooth and shiny. The mediastinal lymph glands were enlarged.

The heart was small, weighing only 200 Gm. The muscle was brown-red. The endocardium and the intima of the aorta showed many yellow streaks. The ascending aorta was widely dilated. The valves were free and normal.

The lungs weighed 675 Gm. The right lower lobe was dark red, heavy and wet. From the surfaces made by cutting, a foamy, turbid fluid could be expressed.

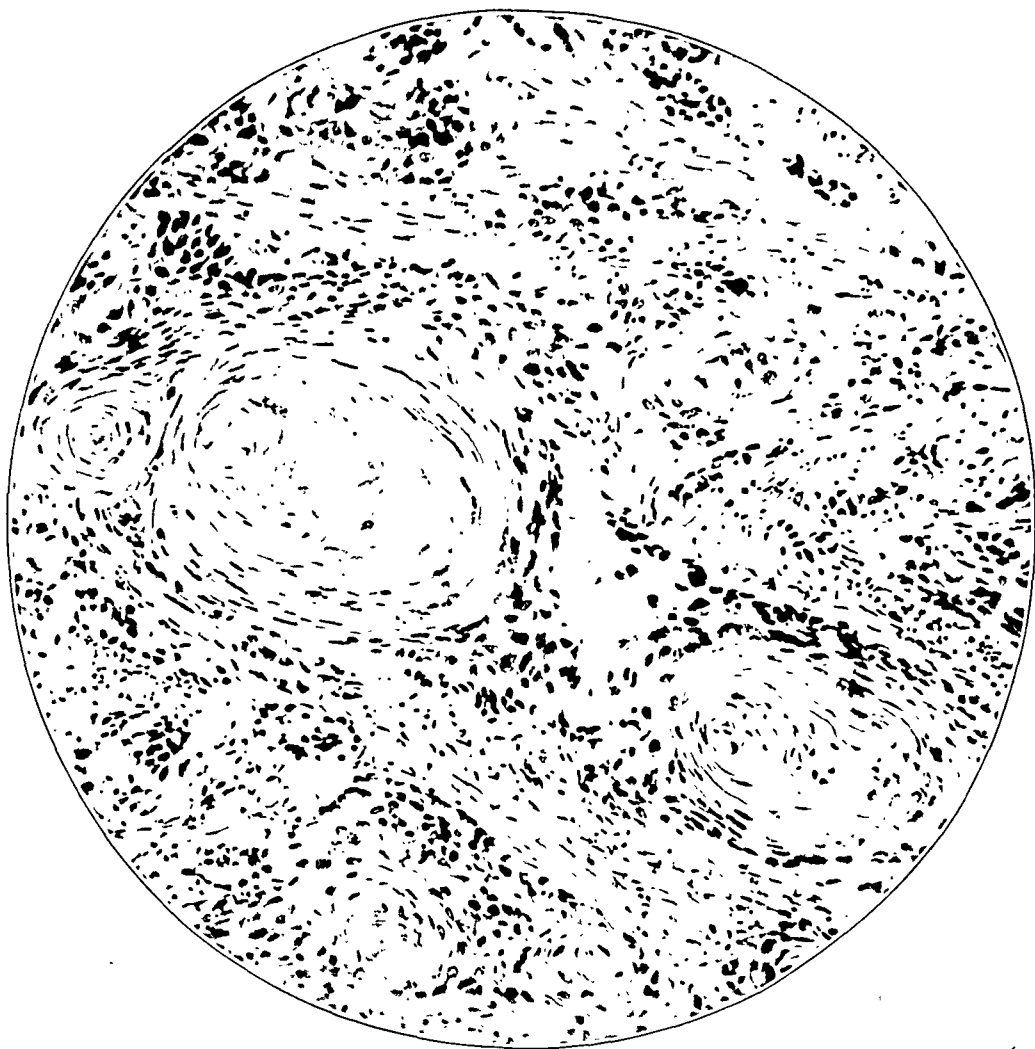


Fig. 2.—Squamous cells with numerous hyaline pearls.

In the small bronchi, purulent fluid was seen. The edges of the lung were blown out.

The tongue was normal; the tonsils were small and atrophic; the larynx, trachea and esophagus were normal; the thyroid was small.

The liver weighed 1,035 Gm., was small and of senile type. The gallbladder was shrunk and filled with a number of brown-black faceted calcium pigment stones. The cystic and common ducts were open.

The spleen was soft and gray-red and weighed 155 Gm. The follicle markings were not visible.

The suprarenals, the pancreas and the stomach and bowels were grossly normal.

The uterus was small and atrophic. The mucosa was red with fresh blood. The ovaries had atrophied. The bladder was filled with cloudy urine. The mucous membrane was red and thickened.

The brain weighed 1,155 Gm. The basilar arteries showed many yellow-white patches.

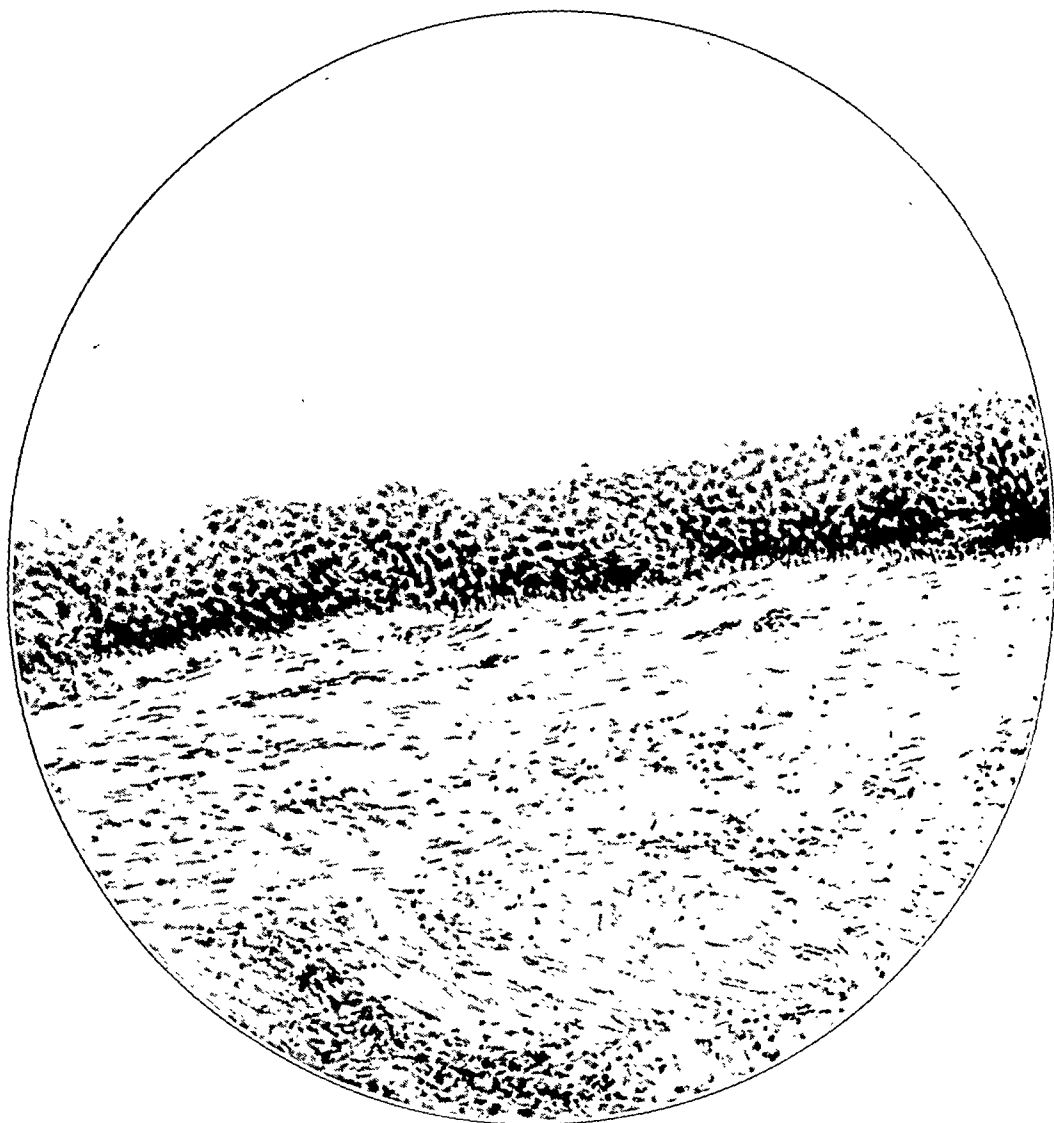


Fig. 3.—Leukoplakia of the renal pelvis.

The right kidney weighed 325 Gm., and measured 11 by 8 by 5 cm. It was embedded in a mass of fibrous tissue, which was firmly adherent to the inferior surface of the diaphragm, to the suprarenal and to the peritoneum about the inferior surface of the liver. The capsule of the kidney was not recognizable. Leading into the kidney from the right flank was the fistula described. On halving the kidney, it was seen that the pelvis and the bases of the calices were filled with an irregular, cauliflower-like, firm mass of grayish-white tumor tissue. This foreign tissue constituted the major portion of the mass, small areas of renal tissue being recognizable grossly only along the margin of the upper and lower poles

(fig. 1). The tumor was attached to the pelvis of the kidney in all but an irregular area approximately 2 by 3 cm. in the inferior portion. The calices were dilated, but their walls collapsed by the pressure of the tumor from within. Clinging to the surface of the pelvis and calices was a grayish-white, putty-like material. After this had been scraped off there came to view a pearly gray, rough, somewhat velvety layer lining the free portion of the pelvis and the calices. This layer was of uneven thickness and could be peeled off, but not without leaving

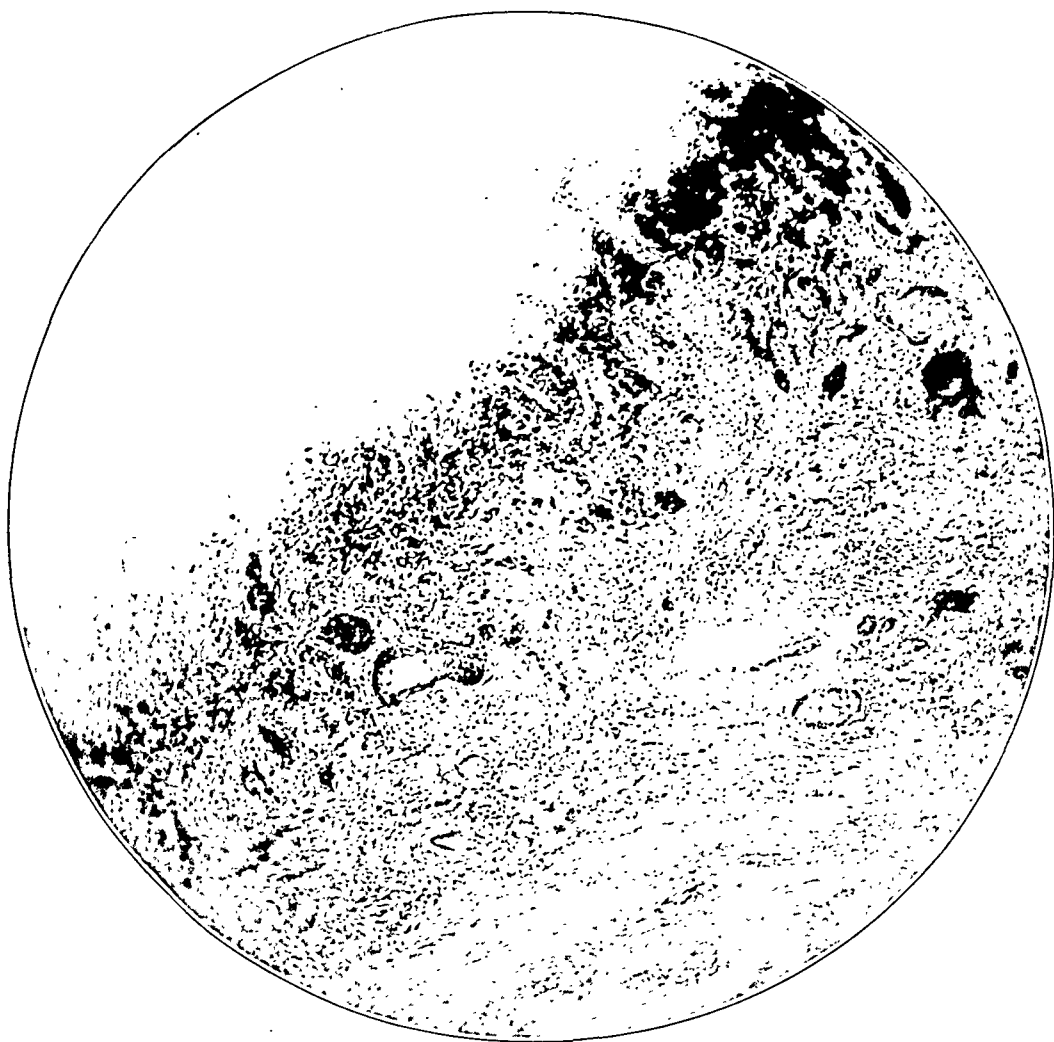


Fig. 4.—Carcinoma cells spreading along the lining of the calix and apparently displacing the leukoplakial layer.

a definitely damaged base. In the tips of several calices could be found small fragments of brown, lamellar calculi from 1 to 5 mm. in diameter.

The left kidney weighed 160 Gm., and was gray-brown and soft. The capsule stripped easily and left a smooth surface. The pelvis and calices were dilated and filled with cloudy urine. The pelvic lining was inflamed. The parenchyma showed signs of degeneration, but no abscesses.

*Microscopic Examination.*—In sections taken from the center of the tumor and stained with hematoxylin and eosin, one saw an irregular growth of cancer cells

in a heavy fibrous tissue stroma. These cells were of the typical large, pale, squamous type. There were numerous areas in which the cells were arranged in whorls, forming as typical epithelial pearls as one sees in a carcinoma of the skin. Some of these pearls had structureless centers of hyalin stained a homogeneous pink (fig. 2).

Sections taken from the calices and the pelvis and stained with hematoxylin and eosin showed that everywhere the lining epithelium consisted of typical squamous cells, in some places a few cells thick, in others many cells thick (fig. 3). Beneath this layer everywhere was a marked infiltration by round cells. Nowhere was normal epithelium found.

A section taken from one of the calices (fig. 4) showed how the malignant growth apparently spread along and displaced the leukoplakial layer of cells.

Microscopic examination of the material in the calices revealed nothing but a structureless debris.

Sections taken from the left kidney and stained with hematoxylin and eosin and sudan III showed marked fibrous and fatty changes as a sequel to a long-standing pyelonephritis.

*Anatomic Diagnosis.*—The anatomic diagnosis was: squamous cell carcinoma of the pelvis of the right kidney; leukoplakia of the pelvis of the right kidney and calices; healed nephrotomy wound with urinary fistula on the right side; pyelitis and pyelonephritis of the left kidney; compensatory hypertrophy of the left kidney; purulent cystitis; edema of the lungs; purulent bronchitis; senile arteriosclerosis; senile dilatation of the aorta; hyperplastic spleen, and brown atrophy of the heart.

#### COMMENT

Why leukoplakia should be so rare when irritation by stone and infection is so common is difficult to explain. The simplest answer that satisfies rather than explains is that nature's tendency is to produce like cells from like. Only under unusual circumstances can any variation occur. The theory of displaced cell remnants might from an embryologic standpoint apply to the urinary tract, but would hardly explain the occurrence of squamous cell changes in the gallbladder or in the pancreas.

The mechanism of cell variation has been designated by most pathologists as metaplasia. The word metaplasia signifies an adaptation on the part of the cells to an altered environment (Adami and McCrae<sup>7</sup>) or a chemical alteration of the cells due to mechanical stimuli (Wells<sup>8</sup>). Metaplasia is a bridge from one type of epithelium to another. How the crossing is made is still a matter of conjecture. Aschoff<sup>8</sup> divided the process into two phases: first, the neoplastic phase or the stage of incomplete cell differentiation; second, the metaplastic phase or the stage of completed cell growth.

7. Adami and McCrae: *General Pathology*, ed. 2, Philadelphia, Lea & Febiger, 1912, p. 202.

8. Aschoff, L.: *Allgemeine pathologische Anatomie*, ed. 3, Jena, Gustav Fischer, 1913, p. 616.

Direct metaplasia, i. e., a change of adult tissue with persistence of the cells, is not likely. It is hardly conceivable that a cell that has gone to maturity can alter its complex chemical structure and become transformed into another type. The change must occur in the plastic, embryonic stage.

Metaplasia, wound healing and tumor development are apparently closely related. In metaplasia, specifically in the case under consideration, leukoplakia of the urinary tract, there is as the initial stage an irritation of the transitional epithelium by stone or infection or by both. This trauma with consequent cell destruction calls for repair. Because of the altered condition there develop occasionally instead of the normal, transitional cells, squamous cells. Lubarsch,<sup>9</sup> Herxheimer,<sup>10</sup> Aschoff<sup>8</sup> and others have ascribed this to a response of the embryonic reserves or cell potentialities. Unusual circumstances bring out and develop this reserve power. A uterus that has been everted and exposed to the air develops squamous epithelium and horny pearls. In ectopia vesicae, squamous cells develop on the surface of the exposed epithelium, and cylindric and mucus-producing cells develop in the depths of the folds of the mucous membrane. This power of adaptation to altered environment is possessed only by the supporting and covering tissues. In specialized tissues with higher functions, adaptation is impossible, and repair can be effected only through the medium of connective tissue.

In the healing of wounds, the mechanical part of the process is similar. After the injury there is an immediate response on the part of the organism to repair the damage. Irritants, named by Carrel<sup>11</sup> "trephones," are released from the leukocytes and lymphocytes and stimulate the embryonic reserves to activity. New cells appear either because they have been stimulated to grow, or because the resistance to growth has been removed. The gap is filled with tissue of similar character or with simple connective tissue. The process is complete and stops abruptly.

In case of tumor development—if trauma is a factor, and it appears to be—there is, following an injury, however slight, an ill fated attempt on the part of the inherent growth forces to repair the damage. The result is a cancer. The more these new uncontrolled cells vary from the adult type which should have been produced the more malignant the tumor is. Why irritation should be followed by normal healing in one case, by the development of foreign cells in another and by the

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9. Lubarsch, O.: Die Metaplasiefrage und ihre Bedeutung für die Geschwülstlehre, Arb. a.d. path-anat. Abt.d. K. hyg. Inst. zu Posen, 1901, p. 205.

10. Herxheimer, G.: Ueber heterologe Cancroide, Beitr. z. path. Anat. u. z. allg. Path. 41:348, 1907.

11. Carrel, A.: Leukocytic Trephones, J. A. M. A. 82:255 (Jan. 26) 1924.

production of cancer in the third is an unsolved problem which is occupying the time of scores of investigators.

Leukoplakia of the urinary tract is not, I believe, the intermediate stage between transitional epithelium and cancer. If the theory of metaplasia is accepted as a change in the embryonic reserves of the tissues, these adult cells must be looked on as end-products, no more capable of differentiating. If irritation were removed from these cells, they might remain as harmless islands of tissue no more apt to undergo carcinomatous changes than other normal tissues.

The islands of squamous epithelium found in the otherwise normal genito-urinary and respiratory tracts may be the result of an earlier metaplastic change that occurred as the result of a temporary inflammation. However, if irritation continues, there is a constant stimulation of the growth forces of these cells and finally an abortive attempt at repair, or cancer.

#### HISTOLOGIC STUDIES

An attempt was made to find squamous epithelium in the normal and in the infected urinary tract not showing leukoplakia grossly. A hope was entertained of finding some intervening stage between transitional and squamous epithelium. Twenty-six urinary tracts were studied. They included: fifteen normal tracts; one tuberculous; two bladders hypertrophied as a result of prostatic obstruction; two dilated infected bladders; one bladder presenting simple cystitis; one, hemorrhagic cystitis; one, chronic cystitis with stones; two urinary tracts showing hydronephrosis and hydro-ureter, and one ureter showing a primary carcinoma. Blocks of tissue were removed from the vesico-urethral junction, trigon, ureteral opening, fundus, ureter and renal pelvis. In 354 sections examined, no squamous epithelium was found nor any more variation from the normal transitional epithelium than would be expected in an infected tissue. The mechanism of metaplasia will most probably be solved by tissue culture methods.

#### SUMMARY

An unusual case of squamous cell carcinoma and leukoplakia of the renal pelvis subsequent to stone is reported. It is impossible to state when the carcinomatous change in this case occurred. The large number of epithelial pearls throughout the entire mass suggests a slowly growing tumor. This case showed no signs of metastases anywhere, in contrast to the cases reported by Scholl and Kretschmer,<sup>12</sup> in which early and extensive metastases occurred.

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12. Kretschmer, H. L.: Primary Non-Papillary Carcinoma of the Renal Pelvis, *J. Urol.* 1:405, 1917.

# THE BREAKING STRENGTH OF HEALING FRACTURED FIBULAE OF RATS

## III. OBSERVATIONS ON A HIGH FAT DIET

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In previous papers we presented an original method for the determination of the healing and breaking strength of fractured and unfractured fibulae of rats on a standard diet. From a consideration of the evidence of the close correlation existing between all parts of the skeleton that was presented at that time, the conclusion was reached that the normal strength of bone may vary widely within comparatively short periods of time, that the unfractured fibula of the left leg will gain and lose strength simultaneously with similar gains and losses in the fractured right fibula of the right leg, and that a close relationship exists between variations in the animal weights, the quantity of food that the rats eat and the strength of the fibulae. No attempt was made to evaluate these factors beyond briefly considering the possibility that there may be present in the diet a definite substance that exerts a strong influence on the strength of both normal and fractured bones. In our search for the dietary factors concerned in this phenomenon, we have continued our studies with albino rats on a high fat diet.

The absorption and excretion of calcium and phosphorus on a high fat diet, as well as the extent to which the fat is utilized by the animals, have been studied by a number of workers. However, for our purposes we find their reported results not in accord, although deserving of the most careful consideration for an understanding of our problem.

The normal association between the digestion of fats and calcium and phosphorus is close. Leathes and Roper<sup>1</sup> concluded from work

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The expense of this investigation was defrayed by Davis & Geck, Inc.

1. Leathes, J. B., and Roper, H. S.: *Monographs on Biochemistry: The Fats*, ed. 2, New York, Longmans, Green & Co., 1925.



of their own as well as from the work of Munk, the pioneer in fat studies, that fats are hydrolyzed to fatty acids and glycerol in the small intestine by pancreatic lipase and succus entericus. Bile facilitates the reaction by emulsifying the fat and accelerating the activity of the lipase. The fatty acids largely combine with the available inorganic salts to form soaps, while the remainder remain emulsified. Both forms of the fatty acid are absorbed except for some of the more insoluble soaps, especially those of calcium. Hunter<sup>2</sup> stated that calcium is absorbed as calcium ions, various phosphate ions and molecular phosphates of calcium in solution. Phosphorus is absorbed as protein molecular combinations (phosphoproteins and nucleoproteins) and as lipids or phosphatides. To a lesser extent, Pryde<sup>3</sup> believes, inorganic phosphates may contribute to the bodily store of phosphorus.

The absence of fat from the diet was shown by Burr and Burr<sup>4</sup> to be followed by the appearance of a dermatitis. McAmis, Anderson and Mendel<sup>5</sup> found that fat was necessary for growth, while Holt and Fales<sup>6</sup> found that calcium absorption was definitely retarded by the absence of fat in the diet. On the contrary, Osborne and Mendel,<sup>7</sup> as well as Drummond and Coward,<sup>8</sup> found that the demands for fat were extremely small, and explicable on the basis that fats were necessary vehicles for the fat-soluble vitamins. On the other hand, Settles<sup>9</sup> found that kittens on a high fat diet were approximately 30 per cent larger than the controls on a normal diet, while Levine and Smith,<sup>10</sup> using a high fat diet in which 86 per cent of the available calories were in the form of fat, found that rats could grow efficiently and utilize 98 per cent of the fat fed. They also reported that other workers in this field had found a 95 per cent utilization of a high fat diet in studies on man, dogs and cats. From these facts we may conclude that fats supply the organism with a ready source of energy in a smaller quantity than any other foodstuff, that they supply the fat-soluble vitamins, especially vitamins A and D, that growth is inhibited in their absence from the diet and proceeds normally when they constitute as high as 86 per cent of the available calories in the diet, that on high fat diets an

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2. Hunter, Donald: *Lancet* **1**:897, 947 and 999, 1930.

3. Pryde, John: *Recent Advances in Biochemistry*, Philadelphia, P. Blakiston's Son & Co., 1926.

4. Burr, G. O., and Burr, M. M.: *J. Biol. Chem.* **82**:345, 1929.

5. McAmis, A. J.; Anderson, W. E., and Mendel, L. B.: *J. Biol. Chem.* **82**: 247, 1929.

6. Holt, L. E., and Fales, H. L.: *Calcium Absorption in Children on a Diet Low in Fat*, *Am. J. Dis. Child.* **25**:247 (March) 1923.

7. Osborne, T. B., and Mendel, L. B.: *J. Biol. Chem.* **45**:145, 1920.

8. Drummond, J. C., and Coward, K. H.: *Lancet* **2**:698, 1921.

9. Settles, E. L.: *Anat. Rec.* **20**:61, 1920.

10. Levine, H., and Smith, A. H.: *J. Biol. Chem.* **72**:223, 1927.

average of at least 95 per cent of the fat is utilized, and that fats are essential to the absorption of calcium and phosphorus.

The influence of a high fat diet on the absorption of calcium and phosphorus depends on the utilization of the fats. Givens<sup>11</sup> found that the poor utilization of fats or fatty acids increased the excretion of calcium in the feces and so prevented its absorption even when it was present in the diet in an adequate amount. Holt, Courtney and Fales<sup>12</sup> obtained similar results in studies on young children. We have noted that Levine and Smith found 98 per cent of their high fat diet utilized. Consequently, if the fat was utilized to the same extent in our experiment with albino rats on a high fat diet, we might expect that the absorption of these two elements at least would proceed normally.

Peters and Van Slyke<sup>13</sup> stated in their recent review that the absorption of calcium is, in general, promoted by those factors which tend to keep calcium in solution in the intestines. Substantiating this opinion, Orr<sup>14</sup> as well as Irving<sup>15</sup> stated that during the digestive process an insoluble calcium phosphate is formed, in which the degree of solubility is in direct proportion to the intestinal acidity. Telfer,<sup>16</sup> in studies on infants, found that fatty acids aided the absorption of calcium by increasing the intestinal acidity and therefore accelerating the change of calcium, phosphate, carbonate and soaps into soluble calcium salts. Theoretically, then, we may expect that on a utilizable high fat diet the absorption of the calcium and phosphorus available would be more efficient and complete than on a normal diet, with the result that the breaking and healing strength of normal and fractured fibulae should be favorably influenced.

#### PROCEDURE

The methods used throughout this experiment remained essentially as described in our previous papers. The animals were placed on a Moise and Smith<sup>17</sup> high fat diet at the outset of the study. In addition, 100 mg. of dried powdered yeast was fed every two days. The salt mixture was the same Osborne and Mendel<sup>18</sup>

11. Givens, M. H.: *J. Biol. Chem.* **31**:441, 1917.

12. Holt, L. E.; Courtney, A. M., and Fales, H. L.: Calcium Metabolism of Infants and Young Children, and the Relation of Calcium and Fat Excretion in the Stools, *Am. J. Dis. Child.* **19**:97 (Feb.) and 201 (March) 1920.

13. Peters, J. P., and Van Slyke, D. D.: *Quantitative Clinical Chemistry*, Baltimore, Williams & Wilkins Company, 1931.

14. Orr, W. J.; Holt, L. E.; Wilkins, L., and Boone, F. H.: The Calcium and Phosphorus Metabolism in Rickets, with Special Reference to Ultraviolet Ray Therapy, *Am. J. Dis. Child.* **26**:362 (Oct.) 1923.

15. Irving, Laurence; and Ferguson, John: *Proc. Soc. Exper. Biol. & Med.* **22**:527, 1925.

16. Telfer, S. V.: *Quart. J. Med.* **20**:1, 1926-1927.

17. Moise, T. S., and Smith, A. H.: *J. Exper. Med.* **40**:13, 1924.

18. Osborne, T. B., and Mendel, L. B.: *J. Biol. Chem.* **37**:557, 1919.

mixture that was used in the previous work on the standard diet. It is especially to be noted in this regard that the total salts on this diet were increased 2 per cent over the percentage used in the standard diet. Moise and Smith found that the rats ate less of the high fat diet, and to make the salt intakes on the two diets comparable, they gave more salt on the high fat diet.

At the expiration of one week on the diet all animals were divided into two groups. The first or fracture group was divided into fourteen lots of seven animals each. The right fibula of every animal was then fractured at a point opposite the tibial prominence. Beginning on the sixth postoperative day and continuing at intervals of three days thereafter for the fourteen periods, the entire lot of seven for each period was killed, the right and left fibula then being removed and prepared in the manner previously described. After suitable drying the healing and breaking strengths of the fractured right and the unfractured left fibulae, respectively, were determined.

The second or control group was free from fracture and had been on the diet for one week with the first or fracture group. At the same time that the fibulae were fractured in the first group, the second group was divided

TABLE 1.—*The High Fat Diet*

	Percentage	Calories per Kilo-gram of Food	Apportionment of Total Calories
Casein.....	25	1,025	Protein 13.8
Crisco*.....	65		
Cod liver oil.....	4	6,417	Fat 86.2
Salts.....	6		
	100		100.0

\* Used instead of lard.

into lots of four, and one lot was observed for each of the fourteen periods from the sixth to the forty-fifth postoperative day with the seven rats with fractures for the same periods. The controls thus served as a basis on which to determine the effect of the diet alone on the skeletal system, and particularly on the breaking strength of the fibulae.

In the second paper of this series of studies we established the breaking strength of normal bone in addition to determining the healing strength of fractured fibulae on a standard diet. These data are used throughout our present paper to evaluate the results obtained. Relative metabolic studies on animal weight and food intake, similar to those reported in our first paper, were also prepared for each of the fourteen periods. In addition, representative roentgenograms of the healing fractures were taken, while correlations were again drawn between animal weight, fibular length and fibular strength on the controls on the high fat diet.

## RESULTS

Results were obtained for the control and the fracture groups on the high fat diet as follows:

I. *Controls on the High Fat Diet.*—Correlations between fibular length, fibular strength and animal weight were drawn on these rats in a similar manner to the correlations on the normal normals.<sup>19</sup>

19. McKeown, R. M.; Lindsay, M. K.; Harvey, S. C., and Howes, E. L.: The Breaking Strength of Healing Fractured Fibulae of Rats: II. Observations on a Standard Diet, Arch. Surg. 24:458 (March) 1932.

Determinations of the breaking strength ratios for the left and right fibulae were made, and records of animal weight and food intake were kept on all rats.

A. Correlations: 1. Between Fibular Length and Fibular Strength. The fibulae were divided into length groups as before, and the respective breaking strength of the left and right bones for each rat in each group was placed under its particular division. The arithmetic mean for the left and that for the right fibula were then obtained, as well as the combined mean of both fibulae.

It was noted that as the fibular length increased, the fibular strength increased in direct proportion, or the longer the bone the stronger the bone. This agreed with similar findings on both the normal normals

TABLE 2.—*Correlation Between Fibular Length and Fibular Strength in Controls on the High Fat Diet \**

	Fibular Length									
	2.0 Cm.		2.1 Cm.		2.2 Cm.		2.3 Cm.		2.4 Cm.	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Arithmetic mean.....	310	307	393	402	498	486	524	553	674	596
Combined arithmetic mean.....	309		398		492		539		635	
Normal normal combined arithmetic mean.....	384		450		457		509		None of this length	
Standard control combined arithmetic mean.....	303		308		394		526		482	

\* Refer to table 2a for complete data.

and the standard controls in our second paper.<sup>19</sup> The means obtained for these last two groups have been placed at the bottom of table 2 for comparison.

2. Between Fibular Length and Animal Weight. The same fibular length divisions that were used in the first correlations were used here. Under each division the respective weight of each rat was placed. The arithmetic mean was determined for the division (table 3), and it was again found that the longer the fibula was, the heavier the animal. This agreed with the observations made on the normal normals and on the standard controls, as will be noted when the progression obtained on these two groups is compared with that for the controls, at the bottom of table 3.

From the correlation, it appears to follow that the heavier the rat the longer is its fibula, or vice versa.

3. Between Animal Weight and Fibular Strength. In the second paper of this series we arbitrarily divided the rats into weight groups, and determined the fibular breaking strength of the members of each division. We found that in the normal normals the heavier the animal

the stronger was its fibula. However, when we attempted to reproduce this strong correlation in the standard controls, the weight group of from 251 to 275 Gm. was found to be made up of animals of unsatisfactory character, with the result that although a correlation was shown to exist, it was considerably less than in the case of the normal normals. On the basis of the information gained from these two correlations, we divided the controls on the high fat diet into similar weight groupings, as seen in table 4. From this it became evident at once that the heavier the animal the stronger was its fibula.

TABLE 3.—*Correlation Between Fibular Length and Animal Weight in Controls on the High Fat Diet \**

	Fibular Length				
	2.0 Cm.	2.1 Cm.	2.2 Cm.	2.3 Cm.	2.4 Cm.
Arithmetic mean .....	201	215	256	274	293
Normal normal arithmetic mean .....	209	230	251	284	None of this length
Standard control arithmetic mean .....	214	223	233	278	295

\* Refer to table 3a for complete data.

TABLE 4.—*Correlation Between Animal Weight and Fibular Strength \**

	190-225 Gm.		226-250 Gm.		251-275 Gm.		276-300 Gm.	
	Left	Right	Left	Right	Left	Right	Left	Right
Arithmetic mean .....	333	330	431	454	464	498	604	574
Combined arithmetic mean.....	332		443		481		589	
Combined mean of normal normals.....	401		415		498		564	
Combined mean of standard controls....	296		373		580		516	

\* Refer to table 4a for complete data.

B. Fibular Breaking Strength Ratios: The breaking strength of the right and left fibulae of the four controls on the high fat diet in each of the fourteen observed periods was determined as in the standard control rats previously reported on. Correction by use of the formula  $R = \frac{F}{(10.W)^{2/3}}$  was then made, and the results seen in table 5 were obtained.

Attention is called to the heading of the left hand column of table 5. The controls were not operated on and were free from fractures, but four controls were killed with seven animals in which the right fibula had been fractured and which were killed at intervals of three days from the sixth to the forty-fifth day postoperatively. The words "post-operative day" consequently are more correctly associated with the animals with fractures, but are used here to avoid confusion later.

When the results of table 5 were plotted in figure 1, it was found that the breaking strength ratios of the left and right fibulae were again in comparatively close agreement. In the fifty normal normals reported on in our second paper<sup>19</sup> we found the left fibula to be a ratio of 9

TABLE 5.—*Breaking Strength Ratios of Controls on the High Fat Diet* \*

Postoperative Day Observed	Left Fibular Ratio	Right Fibular Ratio
6.....	244 $\pm$ 10	262 $\pm$ 25
9.....	256 $\pm$ 32	256 $\pm$ 36
12.....	202 $\pm$ 22	208 $\pm$ 18
15.....	225 $\pm$ 30	221 $\pm$ 32
18.....	279 $\pm$ 16	254 $\pm$ 13
21.....	271 $\pm$ 24	324 $\pm$ 35
24.....	201 $\pm$ 20	185 $\pm$ 22
27.....	251 $\pm$ 21	254 $\pm$ 21
30.....	204 $\pm$ 23	213 $\pm$ 22
33.....	298 $\pm$ 6	280 $\pm$ 27
36.....	185 $\pm$ 40	197 $\pm$ 28
39.....	233 $\pm$ 17	225 $\pm$ 16
42.....	233 $\pm$ 20	222 $\pm$ 35
45.....	298 $\pm$ 64	307 $\pm$ 57

\* Refer to table 5a for complete data.

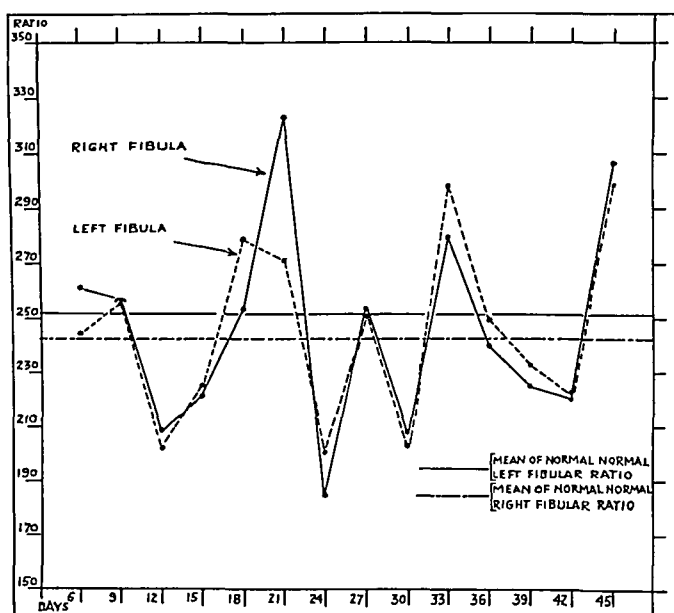


Fig. 1.—The breaking strength ratios of the control group on the high fat diet. These ratios show a greater tendency to remain within the limits of the normal normal band than the ratios for the controls on the standard diet. The average ratio of the left fibulae remains, as in the rats on the standard diet, slightly higher than that of the right.

stronger than the right. When the average from the beginning to the end of the experiment was taken for the controls on the high fat diet, a relatively similar difference was found. On the twenty-first day, recorded in figure 1, the right fibula was considerably stronger than

the left. This result is inexplicable, but is probably due to experimental error in the observations on the breaking strength of the right fibula for that period.

The ratio throughout fluctuated widely. In contrast to the ratios for the controls on the standard diet those for the controls on the high fat diet ended considerably above the normal normal band, and in general the ratios for the controls on the high fat diet showed a greater tendency to be equal to or greater than the ratios of the normal normals. The controls on the standard diet, it will be remembered, presented an irregular but persistent fall in strength below the normal normals.

C. Data on Animal Weight and Dietary Intake: The weights of the rats in each of the fourteen periods were estimated as differences

TABLE 6.—*Animal Weight and Food Intake of Controls\**

Postoperative Day	Difference in Weight from Operation to Death, as per Cent of Weight at Operation	Food Consumed per Day from Operation to Death, as per Cent of Weight at Operation
6.....	— 3.31	1.93
9.....	0.0	2.76
12.....	— 8.85	2.03
15.....	— 6.28	2.78
18.....	— 5.60	2.03
21.....	+ 0.37	2.69
24.....	— 9.55	2.22
27.....	— 8.40	2.37
30.....	—13.72	2.65
33.....	+ 8.50	2.71
36.....	—12.11	3.05
39.....	—12.71	3.01
42.....	— 8.11	2.50
45.....	—15.32	2.13

\* Refer to tables 6a and 6b for complete data.

in the individual weights from the operative day on which observation began to the date they were killed. This gain or loss in weight was determined as percentage of body weight at operation, and is tabulated in table 6.

On the high fat diet the animal weights fell with variations from period to period to the twenty-first day, when the group of four rats for that interval showed a slight gain of + 0.37 per cent. The weights again abruptly fell to a low point of — 13.72 per cent on the thirtieth day. Following this there was a sharp increase in the percentages to + 8.50 per cent on the thirty-third day, with a subsequent drop to a final low point of — 15.32 per cent on the last day.

In figure 2 the percentages have been plotted along with those for the standard controls. One readily sees that though both control groups lost weight, the curve for the standard diet group was much smoother, but that the end-point was considerably lower.

The food intake of these animals fluctuated widely. At first glance, table 6 leads one to believe this untrue, but figure 3 corrects the impression that the tabulated results give. On the contrary, figure 3 shows that the food consumed on the standard diet, although it constantly diminished in quantity, was more uniformly diminished than the amount consumed on the high fat diet. Both diet groups showed an increase on the thirty-sixth day, but differed in that the animals on the high fat diet began to consume more food from the twenty-fourth day, whereas this increase did not begin until the thirty-third day on the standard

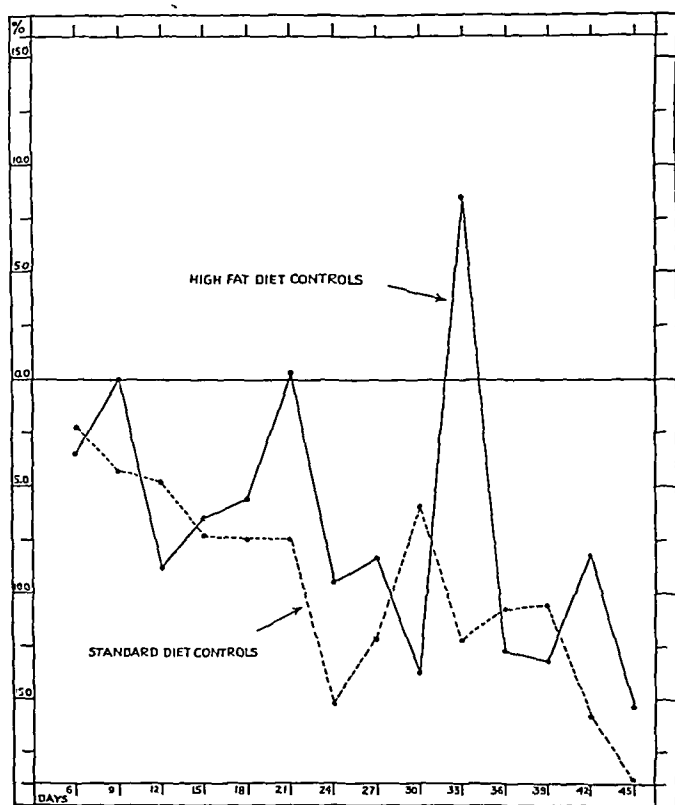


Fig. 2.—The difference in weights from operation to death, plotted as per cent of body weight at operation for controls on the high fat and standard diets. The weights of the controls on the high fat diet fell in a manner not greatly dissimilar to that observed in rats on the standard diet, except that the rate of fall was somewhat slower, and presented more sharply defined variations. It is evident that dietary equilibrium was not attained within the time limits of this experiment.

diet. Both showed a drop thereafter, the standard diet at once, and the high fat diet maintaining its level for another three days, after which it dropped to a point much lower than that reached by the standard diet.

It will be noted at this point that the caloric value of 1 Kg. of the standard diet is 5.340, while 1 Kg. of the high fat diet has a caloric



value of 7.442.<sup>17</sup> Roughly, then, 2 Gm. of the high fat diet has the same potential number of calories as has 3 Gm. of the standard diet. If we interpret the food intake on the basis of its caloric value, we find that the rats, although eating less food in quantity, are actually consuming nearly the same amount of food calorically. Several workers have found that rats tend to balance their food intake by their caloric requirements, and that though they may eat less of one diet than of another, they eat essentially the same number of calories. This appeared well borne out in our results.

II. *Fracture Group on a High Fat Diet.*—The left fibula of each animal in this group was unfractured, while the right was fractured.

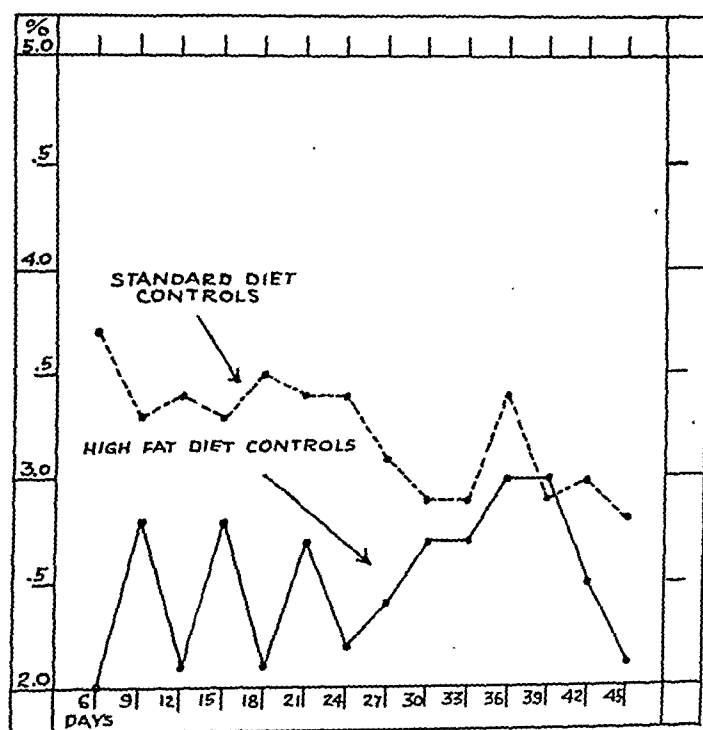


Fig. 3.—Food consumed per day, plotted as percentage of body weight at operation, for controls on the high fat and standard diets. Owing to individual variations in the animals used, the quantity of food consumed fluctuated widely in the early part of the experiment. This was overcome later when the animals had adjusted themselves to the diet. It will be recalled that 1 Gm. of the high fat diet had a caloric value of 7.442, while the standard diet had but 5.340 calories per gram.

Breaking strength ratios were calculated for each bone, and roentgenograms taken of typical calluses in each period. Dietary intakes and animal weights were again recorded, while gross examination of the callus, as reported in our second paper, was dispensed with.

A. *Breaking Strength Ratio of Unfractured Left Fibulae:* The breaking strength determinations on these animals were begun on the sixth postoperative day and continued thereafter at intervals of three

days until the forty-fifth day. The ratios of five animals at least were calculated for each of the fourteen periods.

The ratio on the sixth day postoperatively was  $215 \pm 30$ . It rose slightly to  $219 \pm 22$  on the fifteenth day, fell slightly to  $194 \pm 17$  on the twenty-first day and continued to fall slowly to  $173 \pm 18$  on the twenty-seventh day. It then rose to  $241 \pm 28$  on the thirty-third day, dropped to  $215 \pm 10$  on the thirty-sixth day and finally rose to the highest point of  $261 \pm 26$  on the forty-second day. By the forty-fifth day, the end-point on the standard diet, the ratio had fallen to  $199 \pm 35$ . The ratios are given in table 7.

B. Breaking Strength Ratio of Fractured Right Fibula: Beginning with  $1 \pm 1$  on the sixth day, the ratio rose slowly to a peak on the

TABLE 7.—*Breaking Strength Ratios of the Fracture Group on the High Fat Diet \**

Postoperative Day	Ratio of Unfractured Left Fibula	Ratio of Fractured Right Fibula
6.....	$215 \pm 30$	$1 \pm 1$
9.....	$215 \pm 14$	$75 \pm 26$
12.....	$207 \pm 20$	$107 \pm 10$
15.....	$219 \pm 22$	$112 \pm 9$
18.....	$210 \pm 20$	$84 \pm 7$
21.....	$194 \pm 17$	$80 \pm 9$
24.....	$196 \pm 24$	$74 \pm 17$
27.....	$173 \pm 18$	$125 \pm 4$
30.....	$188 \pm 22$	$126 \pm 27$
33.....	$241 \pm 28$	$153 \pm 31$
36.....	$215 \pm 10$	$146 \pm 13$
39.....	$233 \pm 23$	$149 \pm 15$
42.....	$261 \pm 26$	$201 \pm 30$
45.....	$199 \pm 35$	$108 \pm 26$

\* Refer to table 7a for complete data.

fifteenth day, when it was found to be  $112 \pm 9$ . Thereafter it fell, to reach  $74 \pm 17$  on the twenty-fourth day. Between this day and the thirty-ninth day it rose to  $149 \pm 15$ . Subsequent to the thirty-ninth day it presented a phenomenon previously observed three days later on the standard diet. In both instances there occurred in the space of three days an abrupt rise, which in rats on the high fat diet was from  $149 \pm 15$  on the thirty-ninth day to  $201 \pm 30$  on the forty-second day. In figure 4 it will also be seen that simultaneously with the rapid increase in strength of the healing fractured fibula the strength of the left fibula rose. In addition, figure 4 shows that a similar rise in the ratio of the left fibula occurred on the standard diet. Following the high point on the forty-second day, the fracture strength ratio quickly fell off to reach a low point of  $108 \pm 26$ , at which time this particular phase of the experiment was discontinued.

The curve for the fractured right fibula was both lower and more irregular in rats on a high fat diet than in rats on the standard diet.

After the twenty-fourth day the readings on the high fat diet group fluctuated much more than those on the standard diet group, but their end-points fell well within the standard deviation of each other. The S-shaped curve expressive of the ratio of healing strength was once again evidenced, and was slightly more clearcut than that for the standard diet group.

C. Weight of Rats and Food Intake: The animal weights for the fourteen periods were again estimated on the basis of their difference from operation to death in terms of the percentage of weight at operation (table 8). A slight increase in weight to 0.45 per cent had occurred by the ninth day. This was followed by a decrease in weight to reach

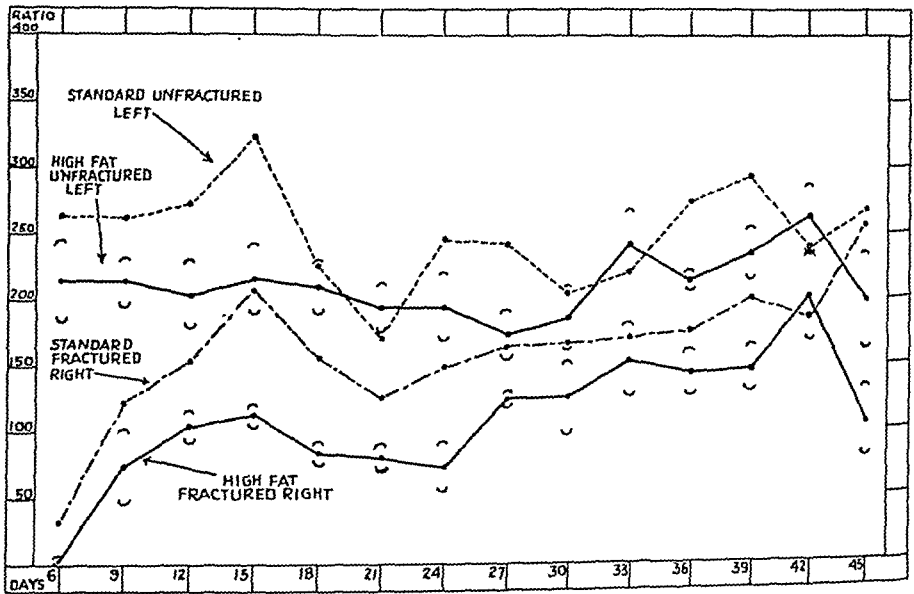


Fig. 4.—Ratio of healing strength of fractured right fibulae and breaking strength of unfractured left fibulae of rats on the high fat diet, with similar ratios for the fibulae of rats on the standard diet. In rats on the fat diet the primary callus had formed by the fifteenth day, as in the rats on the standard diet, but the height of the ratio curve was roughly 50 per cent lower. The decrease in strength simultaneous with the formation of the medullary space, which occurred between the fifteenth and twenty-first days in rats on the standard diet, took three days longer to develop on the high fat diet. The end-point, however, was reached on the forty-second day as compared with the forty-fifth day on the standard diet. The fluctuations in the breaking strength of the left fibula noted in rats on the standard diet, and assumed to be due to a generalized increase in the skeletal salts following the formation of the local provisional callus, did not appear to be so clearly defined in rats on the high fat diet.

—3.34 per cent on the twelfth day. By the fifteenth day, when the primary callus was at its greatest strength, the weight was not only retained but had reached 2.76 per cent. On the eighteenth day the weight was —4.26 per cent, and this loss was regained to attain a

height of 5.15 per cent by the twenty-seventh day. The weight again fell to a low point of — 4.92 per cent on the thirty-sixth day, and ended with a quick rise to 13.08 per cent on the forty-second day, followed by a partial loss of the rapidly gained weight to 6.19 per cent. It is of value to note that simultaneously with the sharp gain in weight on the forty-second day there was a similar abrupt increase in the healing strength ratio of the fractured right fibula. In addition, it will be shown that there was a corresponding increase in the quantity of food that the rats ate.

The food intake of the fracture group on the high fat diet was tabulated as food consumed per day from the operation to death on the basis of its percentage of the weight of the animal at operation (table 8). This was identical with the previous methods of tabulation.

TABLE 8.—*Animal Weight and Food Intake of Fracture Group\**

Postoperative Day	Difference in Weight from Operation to Death, as per Cent of Weight at Operation	Food Consumed per Day from Operation to Death, as per Cent of Weight at Death
6.....	0.0	3.16
9.....	+ 0.45	1.97
12.....	— 3.34	2.72
15.....	+ 2.76	2.71
18.....	— 4.26	3.31
21.....	+ 1.83	2.97
24.....	+ 0.86	2.62
27.....	+ 5.15	2.46
30.....	+ 2.42	2.37
33.....	— 3.86	2.18
36.....	— 4.92	2.75
39.....	— 0.79	2.50
42.....	+13.08	3.50
45.....	+ 6.19	2.72

\* Refer to table 8a for complete data.

It is especially apparent from the results that the increases and decreases in animal weight followed roughly by three days a corresponding increase in food intake. At first thought, this appears unusual, but an increase in the amount of food consumed does not necessarily mean a rising weight curve, any more than does the reverse of this statement. The utilization of the food, of its caloric value, on the contrary would be expected to show its effects on weight. A large quantity of food might be ingested but not digested. It might be lost as an available source of energy and increasing weight by diarrhea. In the early part of the experiment until at least partial equilibrium had been established the stools were loose, fatty and frequent. Subsequent to the eighteenth day this condition was noted to have ceased, and thereafter the weight increased in spite of a diminished intake. On the thirty-third day the weight was — 3.86 per cent. On the thirty-sixth day the food ingested was 2.75 per cent, a gain of 0.57 per cent, while in the same interval the

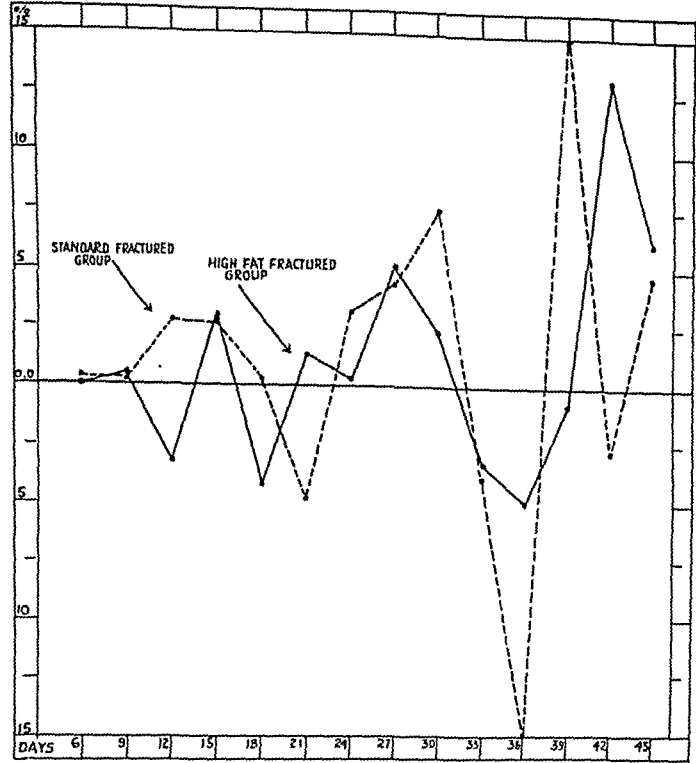


Fig. 5.—The difference in weight from operation to death, plotted as percentage of body weight at operation, for fracture groups on the high fat and standard diets. A rough agreement in the animal weights between the high fat diet and the standard diet groups is observed. The early increase in weight seen in the standard diet group, and due possibly to the increased metabolism following the fracture, was not so apparent in rats on the fat diet. The refusal of the animals to eat during this interval probably accounts for the loss in weight.

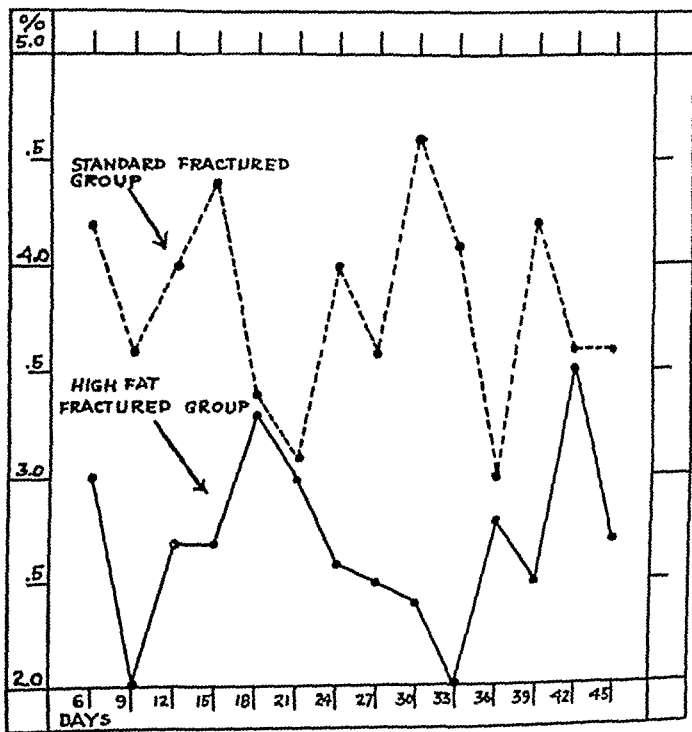


Fig. 6.—Food consumed per day, plotted as percentage of body weight at operation, for fracture groups on the high fat and standard diets. For the first nine days postoperatively the diet was not well tolerated. The ether anesthesia used during the fracture procedure may be at least a partial explanation of this. A positive correlation between the animal weights and the food intake will be noted when this chart is compared with figure 5.

weight fell from  $-3.86$  to  $-4.92$  per cent, a loss of  $-1.06$  per cent. By the thirty-ninth day both weight and food intake were rapidly rising in the first instance and diminishing slightly in the second. Each had sharply risen by the forty-second day (figures 5 and 6).

There seems little reason why one should doubt that with 96 per cent utilization of this diet, as Moise and Smith found,<sup>17</sup> animal weight should vary within limitations directly proportional to the quantity of food consumed. The stimulating effect of the injury and the quickened metabolism, associated with the reparative process, as seen in the plotted curve

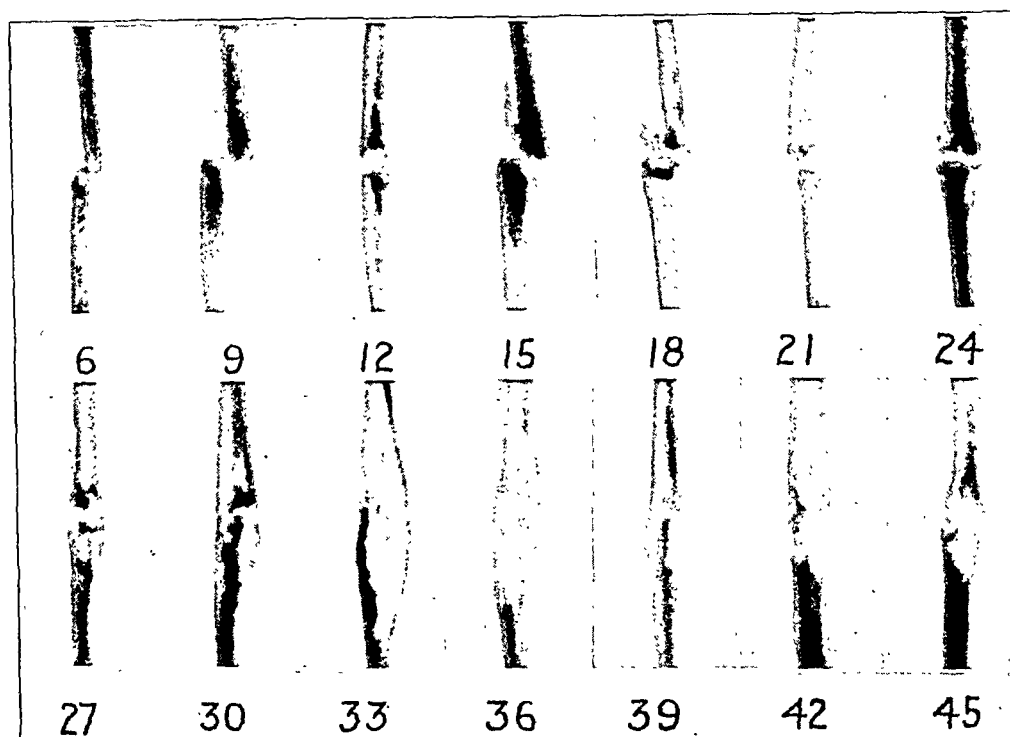


Fig. 7.—Roentgenograms of representative fractures in rats on the high fat diet do not show the reparative process as clearly as those of fractures in rats on the standard diet; however, the resorption of the fragment ends, the increasing size of the callus in the early stages of healing, the development of the medullary space and the modeling of the union are all to be seen. The apparent malposition of the fracture during the first two days is due to separation of the fragments during the drying over anhydrous calcium chloride;  $\times 3.5$ .

for the fracture group on the standard diet (fig. 5), undoubtedly did not occur with much facilitation on the high fat diet. It did occur by the fifteenth day, as may be seen, but it followed a loss on the ninth day. That this loss was due purely to the diet we have little occasion to question. After the fifteenth day the two curves of animal weights for the standard and high fat diets showed a remarkable similarity when the decided difference in the diets is considered.

The food intakes (fig. 6) did not show the same relation to the animal weights on the high fat diet that they did on the standard diet. The intake on the high fat diet was lower throughout than that on the standard diet; yet if the caloric differences in the two diets are considered, a truer picture is obtained. One gram of the high fat diet has a caloric value of 7.442 calories, while 1 Gm. of the standard diet has a value of only 5.340 calories. Consequently the rats roughly need to eat 3 Gm. of the standard diet to get the same number of calories that 2 Gm. of the high fat diet would supply. This goes far to explain the differences in the results, but by no means explains all of them.

D. Roentgenographic Studies: We note that the primary callus was well formed by the fifteenth day, and it will be recalled that the callus was also well differentiated by the fifteenth day on the standard diet. Subsequently the degrees of density observed in the roentgenogram from interval to interval are indicative, to some extent at least, of the formation of the medullary cavity, cortical thickening and reorganization of the callus (fig. 7). Attention is again drawn to the fact that the density of the callus is not a true index of strength after the fifteenth day.

#### COMMENT

The value of the correlations drawn between the body weight, the fibular length and the fibular strength lies primarily in its demonstration of the dependency of these variables on one another. The existence of this interdependency has been suspected for some time, but the data obtained in this as well as in our second paper offer us further substantial evidence of its presence.

In the introduction to this paper the possible effect of a high fat diet on the healing of fractures was considered. The influence of such a diet on the absorption of calcium and phosphorus was our first concern. If these salts determine the strength of the callus to the extent that many believe, it should follow that any change from normal bone strength is indicative of either one of two things: First, absorption of the salts may be within normal limits and the necessary quantity available for the reparative process consequently satisfied, or—owing to a partial or complete failure of one or more of the factors associated with the calcium and phosphorus salts in the formation of the callus, such as the presence in the diet of accelerating or inhibitory substances, i. e., phosphatase or parathyroid—the salts may not be utilized, and the curve of healing strength of the fracture may be considerably below the level set by the fracture group on the standard diet. Second, the salts themselves may be insufficient, owing to a partial or complete failure in their absorption.

The changes recorded in the breaking strengths of the unfractured right and left fibulae of the controls on the high fat diet go far to demonstrate the effect of the diet on normal bone. The fibular strengths fluctuated widely throughout the experiment; however, the trend of the curve is not one of constantly diminishing strength as it was in the case of the controls on the standard diet, but on the contrary is one of increasing strength. Losses are balanced by gains, with the result that the one compensates for the other, and the average for all observations is equal to or slightly greater than normal. It would appear from this that the salts were present in adequate amounts for the maintenance of normal strength, and that their utilization was somewhat better than it had been on the standard diet. This leaves us with the thought that if the heights attained by the healing strengths of the fractures of rats on this diet were lower than those reached by the fractures of rats on the standard diet, it is not due to less calcium and phosphorus being available, but rather to a failure in other factors associated with calcification.

The primary callus in the fractured right fibula was formed, as it was in the standard diet group, by the fifteenth day, but it had a strength ratio of only  $112 \pm 9$  as compared with  $208 \pm 13$  for the standard diet group, or a difference of 96. Simultaneously with the appearance of the medullary cavity, strength was noted to decrease on both the standard and the high fat diets, but in the case of the high fat diet the fall was slower and its lowest level was not reached until the twenty-fourth day, which was three days later than the low level for rats on the standard diet. Further, the level for the high fat diet group dropped but 38 points in nine days, while that for the standard diet group dropped 80 in six days. Subsequently the high fat diet curve remained at a lower level than did the standard diet curve until the forty-second day, when the high fat diet curve rose sharply to reach an end-point above the curve of the standard diet group on that day. The end-point for the standard diet group was not reached until three days later when it gained a point about 50 above the height that the healing curve of the fracture group on the high fat diet attained. Calcification on the high fat diet is apparently less complete than on the standard diet, but ossification occurs three days earlier, though the strength developed by it is roughly 50 less than that of the standard end-point. The rapidity of calcification as well as the extent of the process is less on the high fat than on the standard diet, while ossification occurs more quickly but is less complete. The factors concerned in calcification are apparently more influenced by the diet than are those associated with ossification. We have already seen in the data on the controls that the calcium and the phosphorus are



probably available in sufficient quantity, and we are left then to determine what factor or factors other than the salts are inhibited by the diet.

Howes and Harvey,<sup>20</sup> working in this laboratory on the strength of healing stomach wounds in rats on the Moise and Smith high fat diet, found a retardation in healing, which they attributed to the delay in fibroplasia, while Kugelmass and Berg<sup>21</sup> recently reported that the development of fibroblasts in the callus is greatly inhibited by injections of trypsin into the fracture site, and that coincidentally calcification is incomplete. However, although we have found that the proliferation of fibroblasts into the area is somewhat below normal, we have observed in our unpublished histologic preparations that the formation of the cartilage cells clearly is deleteriously influenced by the high fat diet. We have found not only that the chondroblasts are later in appearance and less in number, but that they persist longer as entities than they do in the normal sections with which they were compared. Whether cartilage cells are formed by metaplasia of fibroblasts or not does not concern us at this time except in its possible explanation of the smaller number of chondroblasts seen. It is at least possible that either there is absent, in the high fat diet, a substance stimulating the process of metaplasia, or there is present a substance inhibiting it. Fell and Robinson<sup>22</sup> found in tissue cultures in vitro of avian limb buds that the hypertrophic cartilage cells were the prime source of phosphatase used in the formation of the growing embryonic bone. Kay<sup>23</sup> found that in patients with fractures the blood plasma phosphatase level rose, and we have found in as yet unpublished work that the bone phosphatase increases to the fifteenth day and subsequently slowly returns to normal. In addition, Berg and Kugelmass<sup>24</sup> reported a fall in blood phosphorus and a rise in blood calcium or a state of phosphorization occurring with the early stages of the healing of fractured tibiae in rabbits. This could be taken as evidence of the activity of phosphatase with a reduction in the circulating phosphorus, while on the high fat diet the absence from the healing fracture of the normal number of cartilage cells may be indicative of a corresponding decrease in the amount of phosphatase available, with a slowing up in the process of calcification of the callus. The rate of calcification is apparently unaffected by the diet, but the degree or extent to which it progresses is affected, for the height of the curve on the fifteenth day is, as we noted earlier, lower although at a peak on the

20. Howes, E. L., and Harvey, S. C.: *Yale J. Biol. & Med.* **2**:285, 1930.

21. Kugelmass, Newton; and Berg, Richard N.: *Ossification*, *Am. J. Dis. Child.* **41**:236 (Feb.) 1931.

22. Fell, A. B., and Robinson, R.: *Biochem. J.* **23**:767, 1929.

23. Kay, H. D.: *J. Biol. Chem.* **89**:249, 1930.

24. Berg, Richard N., and Kugelmass, Newton: *Ann. Surg.* **43**:1009, 1931.

same day as the standard diet level. In other words, the quantitative calcific reaction is subnormal because the chondroblastic phosphatase is less in amount owing to fewer chondroblasts being present.

In the strength curve of the unfractured left fibulae in rats on the standard diet we noted that the strength fluctuated simultaneously with similar variations in the strength of the healing right fibulae. This was again seen in the left fibulae of rats on high fat diet, but to a much lower degree. It is at least possible that the decalcifying powers of the parathyroid hormone as well as the calcifying ability of phosphatase are inhibited by the fat diet. Again, it may be that the extent to which decalcification takes place in the fracture and in the skeleton in general is dependent on the extent to which calcification has advanced. Phosphatase and the hormone of the parathyroid may, in other words, be antagonists, as was suggested in the second paper of our series.

The tendency throughout present day scientific literature to consider calcification and ossification as interchangeable terms appears to us to be unwarranted. Calcification consists essentially in the deposition in bone of calcium carbonate and calcium phosphate, but may occur pathologically at other points as well, while ossification manifests itself in the transformation of the calcific mass into true bone by the action of specialized bone cells, such as the osteoblast, and by the formation of the intricate histologic structure seen in mature bone. Ossification probably is dependent on calcification, but assuredly calcification is not dependent on ossification.

Turning to the end-point reached by the healing fracture on the forty-second day, we are confronted with the fact that union apparently was complete three days before it had been attained on the standard diet. However, it was noted that the strength reached was about 40 below that of the standard end-point three days later. In addition, it is evident that the dictum that the end-point is to be considered as having been gained when the strength is equal to that of the normal bone, as determined by the normal normal rats in our second paper, is untrue, for the diet may be so deficient that normal strength never will be regained. Instead, we may say that the highest point in the curve reached by the healing fracture within the time limit set by the standard diet group, forty-five days, is probably a closer expression of the end-point than is the normal normal. The value of the normal group lies primarily in the earlier postoperative observations of the healing strength, for by comparison with the normal group at that time the extent of the variations are more clearly shown than when they are compared only with the fluctuations seen in the standard diet group at the same time. The sharp drop in strength in both the fractured right and the unfractured left fibulae subsequent to the forty-second day is at present inexplicable, but

fractures on this and other diets are being studied as late as the ninetieth postoperative day in an attempt to find the meaning of the fall.

Although calcification and ossification do go hand in hand throughout the reparative state, and even though it is difficult if not impossible to separate each into clearly defined stages, yet there are intervals in which one will predominate over the other. Calcification is at a peak by the fifteenth day, but ossification is found to be progressing rapidly at the same time. Subsequently ossification increases until it plays the major rôle. The cytologic elements involved are too uncertain for one to draw definite conclusions, but apparently osteoblasts, osteoclasts and other cells are related in some manner to the formation of the osseous tissue. By what means the end-point was reached three days earlier on the high fat diet we do not know, but whatever the stimulus was that resulted in earlier ossification, it was too weak to produce a reaction of sufficient strength to equal that of the end-point of the standard diet level on the forty-fifth day. Possibly the stimulus was sufficient, but the retardation in calcification noted before prevented a complete reaction.

The body weights of the controls on the high fat diet fell throughout the experiment, except on the thirty-third day. However, the weights were consistently greater, and did not fall as low as they did in the controls on the standard diet. Food intake in these rats was less than in the standard diet group, as well as more irregular from interval to interval, but when we note that it takes roughly but 2 Gm. of the high fat diet to give the same caloric value as 3 Gm. of the standard diet, we find a situation entirely different from that we had expected. It was found, several years ago, by different workers that rats tend to consume only enough of any given diet to give them the required calories. Thus we should expect and did find that the animals on the high fat diet ate about the same number of calories on the high fat diet as they did on the standard, although the quantity of food actually consumed was less.

The animals with fractures showed a similar agreement between the number of calories ingested on the high fat and on the standard diets. In addition, they afforded additional evidence of the relatively close agreement between the animal weights, the food consumed and the breaking strength of the fibulae. This was possibly more clearly shown in the controls, but nevertheless was evident here also. The stimulating effect of the fractures, which was followed by an increase in the body weights and in the amount of food taken by the rats, observed to occur in the fracture group on the standard diet up to the fifteenth postoperative day, did not take place in the same fashion in rats on the high fat diet. On the contrary, there was a loss in weight and a diminution in the food intake on the twelfth day, but this was followed

by a rise on the fifteenth day that reached a height slightly greater than that for the standard diet group. The observations on this interval may be at fault, for both before and subsequent to the twelfth day the two diets paralleled each other comparatively closely in respect to the weights of the animals on the diets.

#### SUMMARY

1. Albino rats between 190 and 300 Gm. in weight on a Moise and Smith high fat diet showed a fluctuating normal fibular breaking strength ratio. This varied with the length of time that the animals were on the diet, but ended considerably above the normal breaking strength ratio.

2. The body weights and the quantity of food consumed by the fracture-free controls diminished throughout the experiment. The losses were in practically all cases noticeably less than those seen on a Moise and Smith standard diet.

3. The diet was well tolerated by the animals after the first week.

4. A series of rats in the same age and weight group and on the same diet for the same time had their right fibulae fractured.

5. The primary callus was formed by the fifteenth day, as it was on the standard diet. However, its strength had been attained more slowly, and did not reach such a height as did the callus of rats on the standard diet.

6. The drop in strength, occurring simultaneously with the appearance of the medullary cavity between the fifteenth and twenty-first days on the standard diet, did not take place on the high fat diet until the twenty-fourth day.

7. The end-point of the fractured right fibula was assumed to have been reached by the group on the high fat diet by the forty-second day, whereas it had not been reached in rats on the standard diet until the forty-fifth day. In each group a characteristic abrupt increase in strength began three days before the end-point was reached.

8. The fluctuations observed to occur in the strength of the unfractured left fibula coincidentally with similar fluctuations in the healing strength of the fractured right fibula in rats on the standard diet took place on the high fat diet but to a lessened extent.

9. The strength at the end-point of the unfractured left fibula in rats on the high fat diet was the same as the strength of the unfractured left fibula in the group on the standard diet, though the first was reached on the forty-second day and the second on the forty-fifth.

10. The animal weight and food intake of the controls decreased throughout, though to a less degree when the caloric differences in the two diets were considered.

11. In the case of the fractured lot the animal weights and quantity of food consumed also changed from interval to interval, but showed a greater tendency to maintain a balance than in the controls. This was a rough parallel of similar findings on the standard diet except that weights were somewhat better maintained on the fat diet.

12. The close relationship between breaking and healing strength and the weight of the rats as well as the quantity of food that they will ingest was again brought out in this study.

13. The value of the roentgenogram up to the formation of the primary callus was again noted. Subsequent to that time it affords an unreliable index of the true callus strength.

14. Explanations for the low strength ratios of the fractured right and the unfractured left fibulae in the fracture group of rats were considered, in addition to the probable reason for an earlier end-point. It was assumed that the difference lies in an increase or decrease of some substance elaborated by the fracture, as the fat-soluble vitamins A and D and the salts of calcium and phosphorus were the same in this diet as in the standard. This assumption was based on the belief that the diet was 95 per cent utilizable, as reported by Smith and Moise, which seemed borne out by our own results in the case of the controls on the high fat diet. The possible relation of this substance to phosphatase and parathyroid hormone was considered.

#### CONCLUSIONS

1. A diet of which fat made up 86.2 per cent of the total calories and which was free from preformed carbohydrates produced in the albino rat, free from fractures, a fibular strength average closely approximating the normal breaking strength as determined in rats on a standard diet.

2. The diet in this control group was well tolerated, but was followed by a progressive loss of body weight and diminutions in the quantity consumed from the sixth to the forty-fifth day on the diet. In each case this loss was somewhat less than had occurred under the same conditions on the standard diet.

3. In the fractured rats on the same diet the fractured right fibula increased slowly in strength to the fifteenth day, when the primary callus was formed. A slight rise in strength over the same elapsed time took place in the unfractured left fibula. Decreasing strength was

seen as the medullary cavity developed in the fracture, and increasing strength as the cortex thickened and the callus reorganized. Healing was assumed to be complete on the forty-second day. The changes in strength in the fractured right fibula were paralleled by those in the unfractured left fibula. The height reached was less than that on the standard diet, but the end-point was attained three days earlier on the high fat diet.

4. The animal weights and food intakes remained more constant than in the controls. Weights especially were well maintained, and roughly agreed with the weights on the standard diet. The breaking strength again was seen to be correlated with the rat's weight and the quantity of food that it ate.

5. The value of the roentgenogram after the fifteenth day as an index of callus strength is once more questioned.

6. The necessity for more detailed knowledge of the factors concerned in calcification was made evident.

#### COMPLETE DATA FOR HIGH FAT DIET

TABLE 2a.—*Correlation Between Fibular Length and Fibular Strength in Controls on the High Fat Diet*

	2 Cm.		2.1 Cm.		2.2 Cm.		2.3 Cm.		2.4 Cm.	
	Left, Gm.	Right, Gm.	Left, Gm.	Right, Gm.	Left, Gm.	Right, Gm.	Left, Gm.	Right, Gm.	Left, Gm.	Right, Gm.
	355	320	350	325	395	370	450	425	650	550
	295	300	200	240	385	435	525	670	530	560
	225	240	260	265	575	510	465	570	690	825
	215	200	530	510	600	625	550	590	625	450
	275	200	505	500	375	360	330	345		
	280	270	355	365	545	560	350	350		
	300	330	325	300	480	465	530	675		
	435	560	400	390	540	510	620	615		
	175	200	300	390	525	500	990	980		
	365	340	385	405	560	520	570	575		
	310	260	510	600			425	445		
	495	420	475	450			430	425		
	275	260	475	445			600	560		
	455	500	475	450			505	520		
	230	285	355	400						
	440	310								
	305	290								
	255	245								
	200	305								
Arithmetic mean .....	310	307	393	402	498	486	524	553	674	596
Combined mean .....	309		398		492		539		635	
Normal normal combined mean	384		450		457		509		None this length	
Standard control combined mean .....	303		308		394		526		482	

TABLE 3a.—Correlation Between Fibular Length and Animal Weight in Controls on the High Fat Diet

	2 Cm., Gm.	2.1 Cm., Gm.	2.2 Cm., Gm.	2.3 Cm., Gm.	2.4 Cm., Gm.
	190	190	230	230	285
	190	190	232	240	285
	190	194	234	250	300
	190	195	235	260	300
	190	205	246	265	
	190	208	265	268	
	190	214	270	270	
	190	215	280	275	
	190	225	280	284	
	190	226	285	286	
	195	232		290	
	196	232		295	
	200	235		300	
	204	240		300	
	215	245		300	
	220				
	220				
	230				
	248				
Arithmetic mean .....	201	216	256	274	293
Normal normal arithmetic mean....	209	230	251	284	None this length 295
Standard control arithmetic mean..	214	223	233	278	

TABLE 4a.—Correlation Between Animal Weight and Fibular Strength in Controls on the High Fat Diet

	190-225 Gm.		226-250 Gm.		251-275 Gm.		276-300 Gm.	
	Left, Gm.	Right, Gm.	Left, Gm.	Right, Gm.	Left, Gm.	Right, Gm.	Left, Gm.	Right, Gm.
	355	320	385	405	550	590	540	510
	295	300	255	245	330	345	525	500
	225	240	395	370	545	560	620	615
	215	200	450	425	480	465	560	520
	275	200	510	600	350	350	850	550
	280	270	475	450	530	675	530	560
	300	330	385	435			990	980
	435	560	575	510			570	575
	175	200	600	625			425	445
	365	340	475	445			430	425
	350	325	475	450			600	560
	200	240	525	670			505	520
	260	265	355	400			690	825
	530	510	375	360			625	450
	310	260	200	305				
	495	420	465	570				
	275	260						
	455	500						
	505	500						
	355	365						
	325	300						
	230	285						
	400	390						
	440	310						
	305	290						
	300	390						
Arithmetic mean .....	332	330	431	454	464	495	604	574
Combined arithmetic mean.....		332		443		481		550
Combined arithmetic mean of nor- mal normals .....		401		415		498		564
Combined arithmetic mean of stand- ard controls .....		296		373		580		516

TABLE 5a.—*Breaking Strength Ratios of Controls on the High Fat Diet*

Post-operative Day	Rat Number	Weight (W)		Force (F)		Ratio (R)	
		At Operation	To (10.W) <sup>2/3</sup>	Left	Right	Left	Right
6	2604	232	175.2	335	435	220	248
	2605	230	174.2	395	370	227	212
	2606	275	196.3	520	675	270	344
	2607	230	174.2	450	425	258	244
Mean	....	...	.....	...	...	244 ± 10	262 ± 25
9	2576	235	176.8	600	625	340	353
	2578	194	155.6	260	265	167	170
	2579	265	191.5	545	590	255	292
	2580	190	153.4	355	320	231	209
Mean	....	...	.....	...	...	256 ± 32	256 ± 36
12	2560	190	153.4	295	300	192	196
	2561	245	181.7	355	400	195	220
	2562	250	193.6	540	510	272	257
	2563	190	153.4	225	240	147	157
Mean	....	...	.....	...	...	202 ± 22	205 ± 15
15	2556	190	153.4	350	325	228	212
	2557	226	172.2	385	405	224	235
	2558	284	200.6	620	615	309	303
	2559	190	153.4	215	290	140	120
Mean	....	...	.....	...	...	225 ± 30	221 ± 32
18	2552	260	189.1	550	590	291	312
	2554	220	169.1	440	310	260	183
	2555	234	176.2	575	510	326	259
	2558	215	166.6	400	290	240	234
Mean	....	...	.....	...	...	279 ± 16	254 ± 13
21	2530	250	184.2	465	570	252	309
	2532	300	208.0	690	825	332	396
	2533	295	205.7	425	445	206	216
	2577	240	179.3	525	670	293	374
Mean	....	...	.....	...	...	271 ± 24	324 ± 35
24	2564	235	176.8	475	445	269	252
	2565	190	153.4	275	200	179	130
	2566	190	153.4	280	270	183	176
	2567	265	191.5	330	345	172	180
Mean	....	...	.....	...	...	201 ± 20	185 ± 22
27	2491	205	161.4	505	590	313	310
	2492	300	208.0	420	425	207	204
	2493	285	201.0	530	560	264	279
	2494	208	162.9	355	265	218	224
Mean	....	...	.....	...	...	251 ± 21	254 ± 21
30	2515	290	203.4	350	350	172	172
	2516	290	203.4	570	575	259	253
	2517	190	153.4	300	320	196	215
	2518	268	192.9	325	350	168	181
Mean	....	...	.....	...	...	204 ± 23	213 ± 22
33	2487	300	208.0	600	560	290	269
	2488	190	153.4	435	560	284	365
	2489	196	156.6	495	420	316	263
	2490	309	208.0	625	450	300	216
Mean	....	...	.....	...	...	298 ± 6	250 ± 27
36	2483	255	201.0	650	550	323	274
	2485	190	153.4	175	200	114	120
	2486	190	153.4	200	240	120	157
	2859	225	171.7	300	390	175	227
Mean	....	...	.....	...	...	156 ± 40	198 ± 28



TABLE 5a.—*Breaking Strength Ratios of Controls on the High Fat Diet*  
—Continued

Post-operative Day	Rat Number	Weight (W)		Force (F)		Ratio (R)	
		At Operation	To (10.W) <sup>2/3</sup>	Left	Right	Left	Right
39	2440	300	208.0	505	520	243	250
	2441	220	169.1	305	290	180	172
	2442	232	175.2	475	450	271	257
	2443	190	153.4	365	340	238	222
Mean	....	...	.....	...	...	233 ± 17	225 ± 16
42	2436	214	166.1	325	300	196	181
	2437	195	156.1	310	260	190	167
	2438	233	175.8	510	600	290	341
	2439	246	182.2	375	360	206	198
Mean	....	...	.....	...	...	223 ± 20	222 ± 35
45	2432	215	166.6	230	285	138	171
	2433	285	201.0	560	520	279	259
	2434	286	201.5	990	960	491	486
	2435	204	160.9	455	500	283	311
Mean	....	...	.....	...	...	298 ± 64	307 ± 57

TABLE 6a.—*Animal Weights and Food Intake of Controls on High Fat Diet*

Post-operative Day	Rat Number	Weight of Rat			Food Consumed	
		At Start	At Operation	At Death	Start to Operation	Operation to Death
6	2604	255	232	238	30	42
	2605	240	230	216	35	20
	2606	290	275	270	41	33
	2607	250	230	212	24	16
Mean	....	259	242	234	33	28
9	2576	242	235	233	41	54
	2578	203	194	205	37	80
	2579	283	265	264	35	53
	2580	206	190	180	26	32
Mean	....	234	221	221	35	55
12	2560	190	190	190	38	58
	2561	260	245	232	30	73
	2562	290	280	256	38	60
	2563	200	190	145	38	30
Mean	....	235	226	206	36	55
15	2556	210	190	176	48	118
	2557	240	226	215	39	57
	2558	280	284	265	70	138
	2559	190	190	180	49	60
Mean	....	230	223	209	52	93
18	2552	260	260	235	38	94
	2554	230	220	220	35	87
	2555	250	234	220	37	94
	2558	224	215	200	28	64
Mean	....	246	232	219	35	85
21	2530	260	250	230	69	105
	2532	300	300	332	54	197
	2533	300	295	300	50	154
	2577	250	240	226	26	155
Mean	....	278	271	272	50	153
24	2564	255	235	220	25	110
	2565	190	190	165	40	125
	2566	190	190	170	46	124
	2567	270	265	242	45	105
Mean	....	226	220	199	42	117

TABLE 6a.—*Animal Weights and Food Intake of Controls on High Fat Diet*  
—Continued

Post-operative Day	Rat Number	Weight of Rat			Food Consumed	
		At Start	At Operation	At Death	Start to Operation	Operation to Death
27	2491	206	205	178	50	111
	2492	300	300	300	43	151
	2493	275	285	260	82	271
	2494	200	208	176	73	107
Mean	....	245	250	229	62	160
30	2515	230	270	260	53	171
	2516	300	290	265	95	261
	2517	190	190	155	46	151
	2518	280	268	200	85	229
Mean	....	265	255	220	70	203
33	2487	300	300	349	60	222
	2488	210	190	176	28	211
	2489	198	196	220	40	179
	2490	300	300	325	62	273
Mean	....	252	247	268	48	221
36	2483	280	285	282	65	247
	2485	220	190	168	47	171
	2486	210	190	130	62	277
	2850	225	225	205	37	283
Mean	....	234	223	196	53	245
39	2440	300	300	220	68	397
	2441	235	220	207	44	274
	2442	255	232	205	39	190
	2443	200	190	190	35	245
Mean	....	248	236	206	47	277
42	2436	220	214	200	40	221
	2437	205	195	184	35	204
	2438	250	232	215	32	224
	2439	245	246	215	30	281
Mean	....	230	222	204	34	233
45	2432	225	215	195	40	210
	2433	285	285	250	40	241
	2434	285	286	238	68	295
	2435	200	204	156	55	200
Mean	....	249	248	210	51	237

TABLE 6b.—*Summary of Animal Weights and Food Intake of Controls on the High Fat Diet*

Post-operative Day	Weight at Operation, Gm.	Difference in Weight from Operation to Death, Gm.	Food Consumed per Day from Operation to Death, Gm.	Difference in Weight from Operation to Death as per Cent of Weight at Operation	Food Consumed per Day from Operation to Death as per Cent of Weight at Operation
6	242	— 8	4.67	— 3.31	1.93
9	221	0	6.11	0.0	2.76
12	226	—20	4.58	— 8.85	2.03
15	223	—14	6.20	— 6.28	2.78
18	232	—13	4.72	— 5.60	2.03
21	271	+ 1	7.29	+ 0.37	2.69
24	220	—21	4.88	— 9.55	2.22
27	250	—21	5.93	— 8.40	2.37
30	255	—35	6.77	—13.72	2.65
33	247	+21	6.70	+ 8.50	2.71
36	233	—27	6.80	—12.11	3.05
39	276	—30	7.10	—12.71	3.01
42	232	—18	5.55	— 8.11	2.50
45	248	—38	5.27	—15.32	2.13
48	238	—26	6.5	—10.92	2.73

TABLE 7a.—*Breaking Strength of Fracture Group on the High Fat Diet*

Post-operative Day	Rat Number	Weight (W)		Force (F)		Ratio (R)	
		At Operation	To (10.W) <sup>2/3</sup>	Left	Right	Left	Right
6	1797	280	198.6	340	10	173	5
	1799	242	180.3	395	...	219	...
	1808	275	196.3	275	...	140	...
	1810	265	191.5	395	...	206	...
	1818	228	173.2	580	...	335	...
Mean	....	...	.....	...	...	215 ± 30	1 ± 1
9	1801	215	166.6	300	275	180	165
	1814	240	179.3	445	85	248	48
	1819	225	171.7	345	...	201	...
	1820	203	162.9	415	90	255	55
	2175	210	164.0	310	175	189	107
Mean	....	...	.....	...	...	215 ± 14	75 ± 26
12	1976	250	184.2	...	260	...	141
	1977	194	155.6	270	130	174	84
	1979	200	158.8	250	170	157	107
	2176	260	189.1	410	243	217	131
	2177	260	189.1	530	185	280	98
	2587	270	193.9	400	160	206	83
Mean	....	...	.....	...	...	207 ± 20	107 ± 10
15	1889	230	174.2	435	...	250	...
	1892	232	175.2	275	255	157	146
	1893	263	190.5	260	170	189	89
	2178	300	208.0	645	225	310	108
	2179	215	161.4	285	160	177	100
	2191	275	196.3	450	225	229	115
Mean	....	...	.....	...	...	219 ± 22	112 ± 9
18	1874	208	162.9	420	...	257	...
	1877	240	179.3	390	130	218	73
	1879	292	204.3	390	160	191	78
	1880	238	178.3	395	125	222	70
	2180	230	174.2	210	200	120	115
	2181	200	158.8	400	130	252	82
Mean	....	...	.....	...	...	210 ± 20	84 ± 7
21	1885	200	158.8	415	105	262	66
	1886	198	157.7	305	135	194	86
	1887	195	156.1	290	135	187	87
	1894	232	175.2	310	90	177	51
	2192	265	191.5	285	215	149	112
Mean	....	...	.....	...	...	194 ± 17	80 ± 9
24	1853	190	153.4	280	95	183	63
	1854	239	178.8	535	160	299	90
	1865	190	153.4	225	30	147	20
	2183	242	180.3	320	100	177	56
	2190	300	208.0	365	290	175	140
Mean	....	...	.....	...	...	196 ± 24	74 ± 17
27	1873	205	161.4	240	210	147	130
	1878	246	182.2	270	210	148	115
	2185	300	208.0	490	250	236	120
	2586	196	156.6	240	210	160	134
Mean	....	...	.....	...	...	173 ± 18	125 ± 4
30	1834	234	176.2	280	...	159	...
	1847	190	153.4	175	170	114	111
	1848	246	182.2	450	370	247	203
	1850	235	176.8	350	245	198	139
	2187	300	208.0	545	110	262	53
	2193	282	199.6	290	...	145	...
Mean	....	...	.....	...	...	188 ± 22	126 ± 27
33	1857	215	161.4	320	125	198	77
	1860	288	202.4	475	665	235	229
	1862	281	199.1	330	345	166	173
	1866	235	176.8	610	110	345	62
	2582	278	197.7	520	250	263	125
Mean	....	...	.....	...	...	241 ± 28	153 ± 31

TABLE 7a.—*Breaking Strength of Fracture Group on the High Fat Diet*  
—Continued

Post-operative Day	Rat Number	Weight (W)		Force (F)		Ratio (R)	
		At Operation	To (10.W) <sup>2/3</sup>	Left	Right	Left	Right
36	1829	200	158.8	290	225	183	142
	1843	222	170.2	425	275	250	162
	2583	230	174.2	375	295	215	169
	2584	280	198.6	420	180	212	90
	2585	286	201.5	430	340	213	169
Mean	....	...	.....	...	...	215 ± 10	* 146 ± 13
39	1833	236	177.3	400	245	226	138
	1846	282	199.6	325	400	163	200
	1849	256	187.1	390	330	208	176
	1863	250	184.2	590	195	320	106
	1870	248	183.2	455	235	248	127
Mean	....	...	.....	...	...	233 ± 23	149 ± 15
42	1821	230	174.2	410	445	235	255
	1822	295	205.7	480	400	233	194
	1826	292	204.3	720	505	352	247
	1832	222	170.2	380	180	223	106
Mean	....	...	.....	...	...	261 ± 26	201 ± 30
45	1830	208	162.9	340	125	209	76
	1831	212	165.0	250	75	152	46
	1838	222	170.2	523	315	308	185
	1844	198	157.7	200	195	127	124
Mean	....	...	.....	...	...	199 ± 35	108 ± 26

TABLE 8a.—*Animal Weights and Food Intake of Fracture Group on the High Fat Diet*

Post-operative Day	Rat Number	Weight of Rat			Food Consumed	
		At Start	At Operation	At Death	Start to Operation	Operation to Death
6	1797	265	280	275	57	65
	1799	250	242	240	86	40
	1808	245	275	268	72	76
	1810	255	265	278	68	46
	1818	220	228	230	54	18
Mean	....	247	258	258	65	49
9	1801	210	215	220	51	41
	1814	235	240	245	40	46
	1819	220	225	220	53	30
	1820	200	208	206	52	32
	2175	208	210	215	52	47
Mean	....	215	220	221	50	39
12	1976	236	250	255	65	76
	1977	190	194	164	34	60
	1979	189	200	198	57	85
	2176	260	260	233	67	58
	2177	260	260	265	76	85
	2587	275	270	268	46	101
Mean	....	235	239	231	58	78
15	1889	205	230	242	62	88
	1892	230	232	230	84	118
	1893	255	263	238	64	70
	2178	300	300	332	76	127
	2179	212	215	232	67	99
	2191	272	275	286	56	116
Mean	....	246	253	260	68	103

TABLE 8a.—*Animal Weights and Food Intake of Fracture Group on the High Fat Diet—Continued*

Post-operative Day	Rat Number	Weight of Rat			Food Consumed	
		At Start	At Operation	At Death	Start to Operation	Operation to Death
18	1874	210	208	160	86	163
	1877	250	240	232	53	92
	1879	280	292	288	90	98
	1880	250	238	230	75	233
	2180	234	230	236	46	104
	2181	200	200	205	57	150
Mean	....	237	235	225	68	140
21	1885	188	200	205	60	127
	1886	192	198	200	40	125
	1887	196	195	203	60	119
	1894	210	232	212	72	127
	2192	260	265	292	70	180
Mean	....	209	218	222	60	136
24	1853	222	190	208	19	144
	1854	255	239	219	42	97
	1865	195	190	187	34	127
	2183	255	242	247	52	145
	2190	297	300	308	47	215
Mean	....	245	232	234	39	146
27	1871	218	220	212	55	142
	1873	225	205	236	30	122
	1878	240	246	255	64	162
	2185	320	300	332	66	197
	2586	200	196	190	44	152
Mean	....	241	233	245	52	155
30	1834	230	234	248	65	148
	1847	192	190	185	22	122
	1848	240	246	250	44	169
	1850	220	235	230	57	127
	2187	300	300	310	46	204
	2193	282	282	300	25	225
Mean	....	244	248	254	43	176
33	1857	220	215	226	45	195
	1860	265	268	298	65	205
	1862	270	281	262	67	174
	1866	240	235	225	42	187
	2582	294	278	236	48	170
Mean	....	258	259	249	53	186
36	1829	200	200	195	42	147
	1843	210	222	218	56	390
	2583	255	230	228	26	170
	2584	290	280	265	42	260
	2585	286	286	256	..	...
Mean	....	248	244	232	42	242
39	1833	228	236	236	49	202
	1846	272	282	266	42	194
	1849	252	256	243	44	237
	1863	240	250	252	54	375
	1870	252	248	264	47	233
Mean	....	249	254	252	47	248
42	1821	210	230	262	55	391
	1822	280	295	333	62	470
	1826	205	292	340	50	329
	1832	212	222	240	48	359
		249	260	294	54	352
Mean	....					
45	1830	195	208	226	45	257
	1831	200	212	212	52	261
	1838	220	222	252	55	254
	1844	190	198	202	45	255
Mean	....	201	210	223	49	257

TABLE 8b.—*Summary of Animal Weights and Food Intake of Fracture Group on the High Fat Diet*

Post-operative Day	Weight at Operation, Gm.	Difference in Weight from Operation to Death, Gm.	Food Consumed per Day from Operation to Death, Gm.	Difference in Weight from Operation to Death as per Cent of Weight at Operation	Food Consumed per Day from Operation to Death as per Cent of Weight at Operation
6	258	0	8.17	0.0	3.17
9	220	+ 1	4.33	+ 0.45	1.97
12	239	— 8	6.5	— 3.34	2.72
15	253	+ 7	6.87	+ 2.76	2.71
18	235	—10	7.78	— 4.26	3.21
21	218	+ 4	6.48	+ 1.83	2.97
24	232	+ 2	6.08	+ 0.86	2.62
27	233	+12	5.74	+ 3.15	2.41
30	248	+ 6	5.87	+ 2.42	2.47
33	259	—10	5.64	— 3.86	2.14
36	244	—12	6.72	— 4.92	2.01
39	254	— 2	6.36	— 0.79	2.57
42	260	+34	9.10	+13.08	5.07
45	210	+13	5.71	+ 6.19	2.91
48	235	+ 3	6.23	+ 1.28	2.67
51	205	+19	6.55	+ 9.27	3.68

# ADAMANTINE EPITHELIOMA

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Adamantine epithelioma has long been known and well described as an entity. Excellent case reports have appeared in the American literature with reviews of continental papers, but no large number of cases has been presented. Because of this and the high percentage of recurrences after a primary operation, a series of thirty-five cases is herein reported together with the discussion of the differential diagnosis of central cystic tumors of the jaws and certain observations on their histogenesis. This series is based on the records of the Surgical Pathological Laboratory of the Johns Hopkins Hospital and includes patients from the wards of the Department of Surgery, from the private clinic of Dr. Joseph Colt Bloodgood, together with a scattering of cases from other sources referred to this laboratory for diagnosis.

The jaws are a region in which both dentistry and surgery overlap with a resulting confusion of the boundaries of specialization. The surgeon is well equipped to attack late, easily recognizable, malignant processes arising in this region. He is not always prepared, however, to differentiate between an early malignant process and the more common dental pathologic changes. The dentist, on the other hand, meets with neoplasms so infrequently that an early case is usually misdiagnosed. Since advanced neoplasms of the jaw are now rarely seen, the surgeon of necessity must learn to recognize atypical pathologic changes in the jaw and to rule out early malignant processes. This is fundamental to the present-day diagnosis and treatment of neoplasms in the region of the jaws.

## THE LITERATURE

No attempt is made here to present a review of the literature on adamantinoma, which begins with Broca<sup>1</sup> (1869), who derived these tumors from the enamel organ, and Malassez<sup>2</sup> (1885), who contributed

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From the Surgical Pathological Laboratory of the Johns Hopkins Hospital and University.

1. Broca: *Recherches sur un nouveau groupe de tumeurs designé sous le nom d'odontomes*, *Gaz. hebdomadaire de médecine et de chirurgie*, 1868.

2. Malassez: *Sur le rôle des débris épithéliaux paradentaires*, *Arch. de physiologie normale et pathologique*, 5:309, 1885.

a fundamental anatomic and pathologic study of the jaws and teeth. Since these early investigations, scattered case reports have appeared. In 1905, Steensland<sup>3</sup> collected twenty-one cases from the literature; in 1910, Lewis<sup>4</sup> stated that there were seventy cases to be found, and in 1924, Murphy<sup>5</sup> estimated the number to be one hundred. From the number of reported cases it might be inferred that the adamantinoma is a very rare tumor. It is not to be doubted, however, that most cases are unrecognized, as Simmons<sup>6</sup> noted in reporting twelve of his own cases. For the most complete bibliography to be found in the American literature the reader is referred to Murphy.<sup>5</sup> Roemer<sup>7</sup> has reviewed the entire literature.

#### CLINICAL COURSE

*Site.*—The site of origin of the adamantinoma is noteworthy, the tumor showing a marked predilection for the lower jaw. Of the thirty-five cases in this series, twenty-nine were of the lower and six of the upper jaw. In the lower jaw the molars are the most frequently affected, and while the specific tooth first encroached on is seldom noted in the history, the site of the third molar was nevertheless mentioned in seven instances. The bicuspsids, canines and incisors are infrequently involved. Only two tumors began anteriorly, one involving the symphysis. The upper jaw is less frequently affected. Of the six tumors in this location, four began anteriorly and two posteriorly. All of them involved the antrum by direct extension. In only one of these cases was the tooth of origin mentioned, the lateral incisor being implicated in this instance.

*Sex, Race and Age Incidence.*—Of the thirty-five patients, eighteen were females and seventeen were males. Scudder<sup>8</sup> and others, however, have noted a higher incidence among women. Fourteen patients were colored and twenty-one white. Since all but one of the patients of Dr. Bloodgood's series, as well as most of those in the referred cases, were white, this is not a representative ratio. The true ratio is to be found in the group of patients from the surgical wards of the Johns Hopkins Hospital. Of seventeen patients, eleven were colored and six were white. The proportion of colored to white patients in the surgical

3. Steensland, H. S.: Epithelioma Adamantinum, J. Exper. Med. **6**:377, 1905.

4. Lewis, Dean: Multilocular Cysts of Jaws, Surg., Gynec. & Obst. **10**:28 (Jan.) 1910.

5. Murphy, J. T.: Adamantine Epithelioma, Radiology **3**:377 (Nov.) 1924.

6. Simmons, C. C.: Adamantinoma, Ann. Surg. **88**:693, 1928.

7. Roemer, O.: Die Pathologie der Zähne, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1928, vol. 4, no. 2, p. 89.

8. Scudder, C. L.: Tumors of the Jaws, Philadelphia, W. B. Saunders Company, 1912, p. 177.



TABLE 1.—Analysis of Thirty-Five Cases

Path. No.	Race	Sex	Age	Jaw Site	Age of Onset	Symptoms of Onset	Duration of Primary Tumor, Years	Number of Recurrences	Duration of Disease, Years	Treatment	Microscopic Observations	Gross Pathology	Results
(S.N. 26)	C	F	50	Upper anterior	40	Pimple roof of mouth	10	0	10	Resection of both sides of upper jaw, 6/24/89	Adult, marked cyst formation	Solid and cystic	Died of shock, 6/24/89
419	W	F	52	Lower	44	Gum boil	4	1	8	Primary removal, recurrence in 3 years; excision with alveolar border jaw, 4/13/94	Adult, marked cyst formation	.....	Well 11/95, for 1 year; then lost from observation
566	W	M	54	Lower angle to symphysis	34	Lump following carious molar tooth extraction	30	0	20	Resection of lower jaw on left, 8/17/94	Undifferentiated	Solid and cystic	Death 4/05 without recurrence; well 11 years
2084	W	F	37	Lower angle	17	Tumor	20	0	20	Resection of lower jaw on left, 1/28/98	Undifferentiated; papillomatous	Solid and cystic	Well 4/03, for 5 years; lost from observation
2977	C	M	20	Lower posterior	14	Tumor	6	0	6	Partial excision of jaw with glands of neck, 3/10/00	Adult	Solid	Well 7/03, for 5 years; lost from observation
4169	C	M	39	Lower angle to symphysis	31	Pain, then swelling	8	0	8	Resection of lower jaw on right, 3/26/02	Undifferentiated; papillomatous	Cystic	Well 8/05, for 3½ years; lost from observation
4359	W	F	40	Lower angle and ascending ramus	28	Lump following carious tooth extraction	5	1	12	Primary excision, 1895; resection of lower jaw on right, 1902	Adult	Cystic	Well 1923, for 21 years; lost from observation
4657	W	F	30	Lower angle	27	Loose molars	3	0	3	Partial excision of lower jaw on left, 5/28/04	Undifferentiated; papillomatous	Cystic	Well 11/04, for 6 months; lost from observation
5094	C	M	28	Lower angle to canine	18	Tumor	10	0	10	Resection of lower jaw on right, 10/9/03	Adult	Cystic	Well 6/04, for 8 months; lost from observation
7348	C	F	45	Lower posterior	44	Tumor	10 mo.	0	10 mo.	Curettage, chemical cautery, 6/1/06	Adult	Solid	Died 1915 without recurrence; well 9 years
9722	C	F	55	Lower angle to symphysis	40	Tumor following wisdom tooth extraction	15	1	20	Primary resection of two-thirds of lower jaw with glands of neck, 4/17/08; well 4 years, then operation for recurrence, 11/20/14	Adult	Cystic	Postoperative death from shock, 11/21/14
10834	W	M	26	Lower at symphysis	18	Premolar extraction followed by swelling	8	0	8	Partial excision with preservation of continuity of jaw bone, 9/12/10	Undifferentiated; few stellate areas	Solid	Well 1/23, for 17 years; living
12213	C	F	36	Upper anterior	29	Swelling and pain	6	0	6	Drainage of antrum, 10/4/11; resection of upper jaw and roof of mouth, 10/24/11	Undifferentiated; papillomatous	Solid	Well 6/15 for 3½ years; then lost from observation

	W	F	23	Lower pos- terior	22	Swelling	1	0	1	Excision, 2/18/13	Adult; marked cyst formation	Monocystic	Unknown; patient lost from ob- servation
13533	W	F	43	Lower pos- terior	19	Swelling	15	2	24	Excision, 1904 and resection of lower jaw on left, 8/23/13	Adult	Solid and cystic	Unknown; patient lost from ob- servation
14700	W	F	41	Lower pos- terior	19	Swelling	(?) mo.	13 plus	29	1893-1902: ten curet- tages and excisions; 1902: resection of lower jaw on left; 1913-1919: repeated excisions, radium treatment	Transitional; marked kera- tinization in areas	Recurrence in temporal fossa re- moved 3/13; solid	Died of tumor, 2/3/21, aged 49 years
17524	W	M	19	Lower angle	13	Swelling	(?) mo.	22 plus	12	1912-1917: six curet- tages and two radium treatments; 1917-1918: repeated cautery and resection of jaw	Adult	Solid tissue in recurrence of 1918	Died of tumor, 1924; aged 25 years
23540	C	F	39	Lower pos- terior	14	Lump following tooth extraction	5	7	15 plus	1908: local excision; 1903-1914: six opera- tions for recurrences; incomplete removal of recurrence extending to base of skull, 12/27/18	Adult	12/27/18, solid	Unknown; patient lost from ob- servation
26151	W	M	53	Lower pos- terior	48	Swelling following molar extraction	1	3	12	Primary curettage, 1917; curettage, 1920; curettage and cau- tery, 1927	Undifferentiated; papillomatous	Cystic	Well 8/30 for 3 years
27496	C	F	13	Lower angle to symphysis	7	Swelling	1	2	11	1915-1916: two lanc- ings; 1920: excision; 1/25/21: curettage; 5/29/26: resection of tumor	Adult	1921: cystic; 1926: cystic	Died 11/6/26 of pneumonia
27505	W	M	50	Lower angle	49	Swelling	5 mo.	1	1	7/22/20: curettage, radium treatment; 2/28/21: resection of tumor, chemical and thermal cautery	Transitional	Recurrence solid with occasional cysts	Well 7/30, for 9 years
27506	W	M	42	Lower angle	32	Swelling	4	2	10	1914: excision of cyst; 1917: incision; 2/15/21: curettage, chemical cautery	Adult	Solid	Well 4/31, for 10 years
28335	W	F	46	Lower pos- terior	33	Pain, then swelling	13	0	13	Resection of lower jaw on left	Transitional; papillomatous	Cystic	Unknown; patient lost from ob- servation
28500	W	M	17	Upper and posterior	15	Tumor following tooth extraction	2 1/4	0	2	Curettage; chemical cautery, 8/13/22	Undifferentiated	Solid	Well 6/30, for 8 years
4404	C	M	30	Lower angle to symphysis	39	Abscessed molar ten years	1	1	4	1920: removal of "in- flammatory tissue"; 10/21/22: resection of lower jaw on right	Adult	Cystic	Well 6/30, for 8 years
55052	C	F	20	Upper anterior	17	Tumor following tooth extraction	3	0	3	1921: radium treat- ment; 6/26/23: radical operation on antrum; electric cautery	Adult	Solid with numerous minute cysts	Well 6/30, for 7 years

TABLE 1.—Analysis of Thirty-Five Cases—Continued

Path. No.	Race	Sex	Age	Jaw Site	Age of Onset	Symptoms of Onset	Duration of Primary Tumor, Years	Number of Recurrences	Duration of Disease, Years	Treatment	Microscopic Observations	Gross Pathology	Results
34188	W	F	29	Lower angle	21	Swelling and "abscessed gum"	6	2	9	1921: curettage; 1923: roentgen treatment; 1/4/24: excision; 9/26/29: excision and drainage; 4/25: curettage, thermal and chemical cautery, 3/11/25 mal and chemical cautery, 1919-1925: four lancetings; curettage, 10/30/25; curettage with chemical cautery, 12/26/25	Adult	Cystic	Well 12/30, for 1 year
36356	C	F	28	Lower anterior	27	"Gum boil"	?	1	6	1926: five roentgen treatments; 1/9/27: curettage, chemical and thermal cautery; 1, 2, 5/27: repeated cauteries	Adult	Solid and cystic	Well 7/27, for 2 years and 4 months; lost from observation
38135	W	F	31	Lower ascending ramus	27	Swelling	19	3	20	1919-1925: four lancetings; curettage, 10/30/25; curettage with chemical cautery, 12/26/25	Transitional	Solid	Well 6/27/30, for 4½ years
38746	W	M	35	Lower angle	16	Swelling	..	2	13	1926: five roentgen treatments; 1/9/27: curettage, chemical and thermal cautery; 1, 2, 5/27: repeated cauteries	Transitional	Cystic	Died of tumor, 12/17/27; 11 months after operation
40822	W	M	..	Lower angle to symphysis	..	"Abscess"	..	..	10	1925: excision; 1921: excision and radium treatment; 1928: wide excision	Adult	Resection, 1925; cystic	Unknown; patient lost
40917	W	F	44	Lower angle to symphysis	24	"Swelling while cutting III molar"	..	..	25	1906-1925: five excisions; 1919: resection of jaw; 1925-1930: repeated excision of recurrences	Adult, atypical	Solid	Discharged with recurrence, 7/3/29; lost from observation
42639	C	M	57	Lower angle	53	Tumor	3	3	2	Incision and drainage; osteomyelitis, 5/9/27; curettage, 11/26/27; excision, 1/13/28; resection of jaw, 5/24/29	Transitional	Cystic	Discharged 1/31, well
42639	C	M	57	Lower angle	35	Tumor noticed in mirror	6 mo. plus	1	6	section of jaw, 5/24/29 of wisdom tooth, 1922: extraction of teeth for neuralgia; 6/25: curettage, cautery	Adult	Solid	Discharged 4/31, well
44222	W	M	41	Lower angle	45	Swelling	1 mo.	0	1 mo.	3/20/31	Adult	Solid	Discharged 4/31, well

wards of this hospital over a twenty-five year period was 1:6. Using this factor, the corrected ratio of colored to white patients is 11:1, demonstrating a significantly high incidence of the adamantinoma among the colored race. This finding corroborates the observation of Graves,<sup>9</sup> who noted that dental tumors were more common in Negroes than in white persons.

The age at which the patient first notices the tumor is usually between 11 and 35 years; twenty-five tumors appeared in this period, while only one occurred earlier and eight later. The extremes of age are 7 and 53 years. Figure 1 compares the age of onset in this series

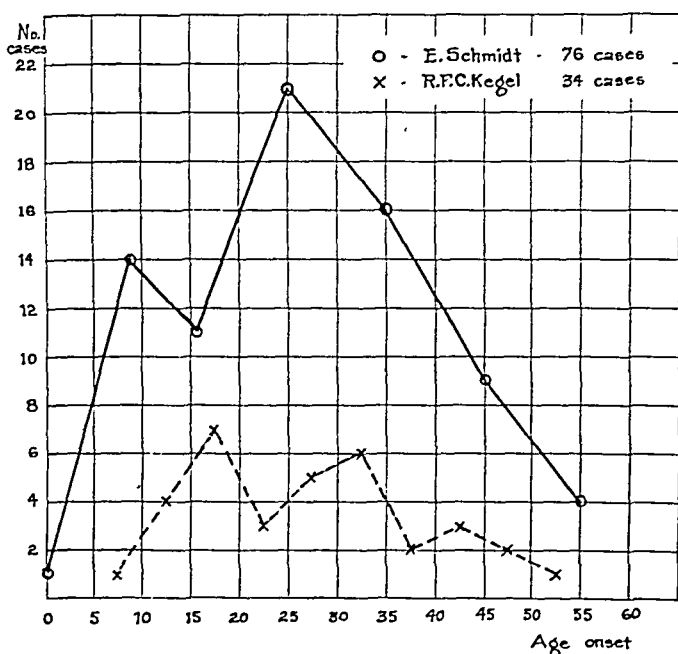


Fig. 1.—Chart showing age of onset of adamantinoma in the seventy-six cases of E. Schmidt and the thirty-four cases of the present series.

with that in the seventy-six cases reported by Schmidt.<sup>10</sup> Eleven cases, approximately one-third, fall in the second decade of life. This period corresponds to the time of eruption of the molar teeth and is also the period of greatest incidence of the dentigerous cyst. Many patients would undoubtedly fall within earlier age groups were it not for the fact that the rate of growth of some tumors is so slow that they remain unrecognized for years.

*Rate of Growth.*—The rate of growth of the adamantinoma is slow, and the duration of the tumor is lengthy. Seven cases showed a dura-

9. Graves, S.: A Case of Adamantinoma Showing Epithelial Pearls. *Am. J. M. Sc.* **154**:313, 1917.

10. Schmidt, E., cited by Roemer (footnote 7).

tion of the primary tumor of fifteen years or more. Occasionally, a recent rapid increase in size in a tumor that had remained stationary for years brought the patient to the hospital for operation. As evidenced by the lengthy duration of the tumors, there is seldom any pain except occasionally in the beginning. It is rather because of the facial deformity that the patient seeks surgical intervention.

*Physical Examination.*—The tumor may be of great size (fig. 2). Growths the size of a fetus' head have been reported. In these days, however, it is rare to see a growth larger than a silver dollar, most patients appearing when the swelling is quite small. On examination, the tumor presents a symmetrical, usually lobulated swelling of the jaw which extends outward and encroaches but little on the buccal cavity. The tumor varies in consistency, depending on the degree of bone expansion. Sensations as markedly different as fluctuation, parchment crep-



Fig. 2 (Path. no. 27496).—Adamantinoma of seven years' duration in a colored girl aged 13.

itation and bony hardness are found. Soft areas later may become bony hard owing to the laying down of reactive bone. These physical signs are characteristic of all central jaw lesions that have reached a size sufficient to expand the bone; none is pathognomonic of the adamantinoma. The signs merely distinguish the periosteal from the central lesions.

The skin over the tumor is not adherent; the mucous membrane is usually intact except when a fistula exists. In this series there was found no evidence of lymphatic involvement, and the lymph nodes were not palpable unless the tumor was infected.

When the tumor has expanded the bone to paper thinness, rupture into the oral cavity occurs, with a discharge of fluid. A discharge was noted in twenty cases. The discharge varied in color from yellow to brown, sometimes blood-tinged, rarely frank blood, and in consistency from a watery to a serous fluid. Following rupture, a fistula usually persists and drainage continues intermittently. In three cases

an osteomyelitis resulted by infection through the sinus, complicating the original lesion so that before operation it was thought to be a simple osteomyelitis of the jaw. The gross pathology at operation, verified by frozen sections, determined the diagnosis.

In the upper jaw, extension into the antrum was almost inevitable, obscuring the clinical picture so that all the tumors of the upper jaw were clinically diagnosed as primary malignant processes of the antrum. Conversely, in our files of adamantinoma there were found cases of

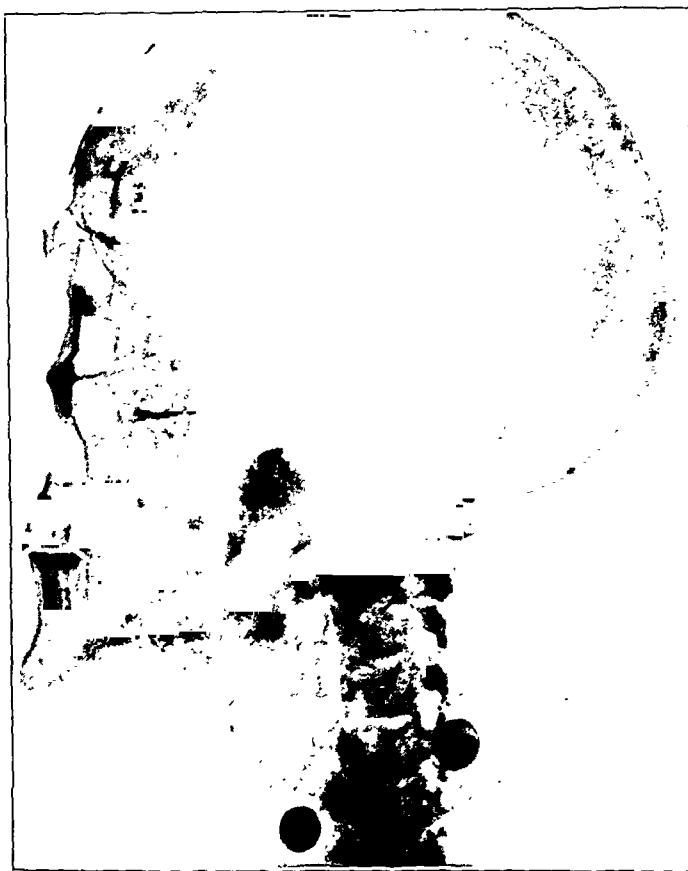


Fig. 3 (Path. no. 40822).—A recurrent adamantinoma producing a polycystic, honeycombed lesion of the mandible.

antrum carcinoma, one of which was reported in the literature as a dental tumor (Murphy). New<sup>11</sup> reported that of 168 malignant processes of the antrum of Highmore occurring in an eight year period at the Mayo Clinic, thirty-nine, or 23 per cent, were malignant processes primary to the upper jaw and secondarily invading the antrum. Carcinoma of the antrum has its highest age incidence after 50 years, and its rate of

11. New, G. B.: Treatment of Malignant Tumors of the Antrum, *J. A. M. A.* 74:1296 (May 8) 1920.

growth is much more rapid than that of the adamantinoma, two fundamental points of differentiation.

*Roentgen Appearance.*—The roentgen appearance of the adamantine epithelioma of the lower jaw is that of a central bone expansive tumor. The bone is bulged outward with clearly demarcated outlines that show none of the fuzziness of osteomyelitis or invasive carcinoma of the gums, nor is there a periosteal reaction. The lesion may be either monocystic or polycystic. A polycystic tumor that produces a honeycombed appearance throughout the entire jaw has been described as characteristic of

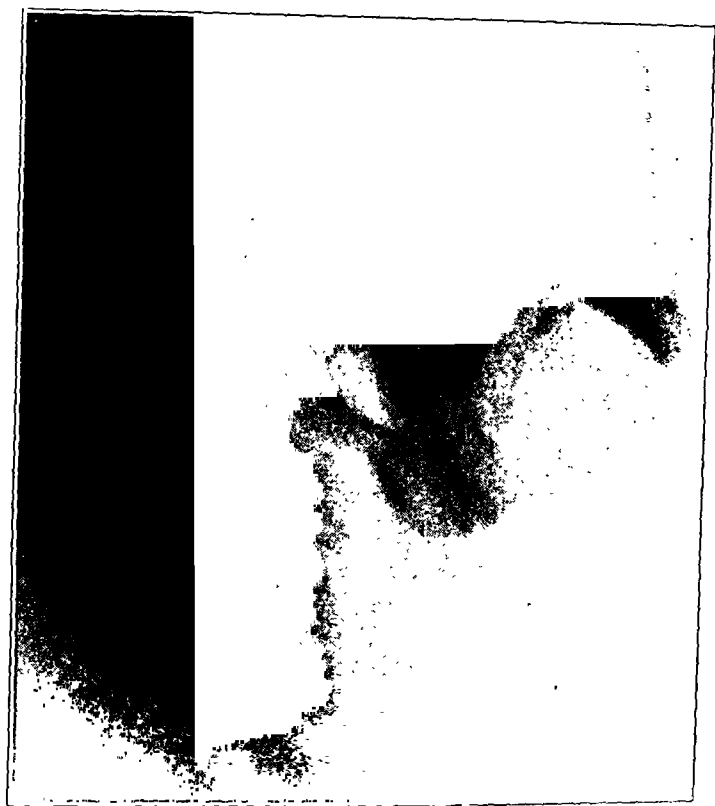


Fig. 4 (Path. no. 3635).—Roentgenogram of an adamantinoma of the mandible. Note the bone expansive polycystic appearance. This is a rare site. (Cf. fig. 5.)

the adamantinoma, although the root cyst and the giant cell tumor may present the same appearance (fig. 3). As I<sup>12</sup> pointed out in a previous paper, dental root cysts of more than from 3 to 4 cm. in diameter, the dentigerous cyst, the giant cell tumor and the central fibroma, are all central bone expansive growths which produce roentgen lesions that cannot always be distinguished one from another and from the foregoing two types of adamantine epithelioma. In most instances the roentgenogram is of value only in distinguishing a central from a periosteal lesion and in ruling out osteomyelitis.

12. Kegel, R. F. C.: Central Tumors of the Lower Jaw, *Radiology* 16:216 (Feb.) 1931.

When the adamantinoma is in the upper jaw, in which position invasion of the antrum invariably occurs, the roentgenogram is of little diagnostic value. The use of injections of iodized poppy seed oil 40 per cent into the antrum has been suggested as an aid in differentiating primary antrum tumors from secondary growths of the jaw. It is of some value when the bulged-in wall of the antrum is still intact.

*Roentgen Diagnosis.*—The small dental root cyst, the end-result of an apical peridontitis, has a roentgen appearance quite typical because of

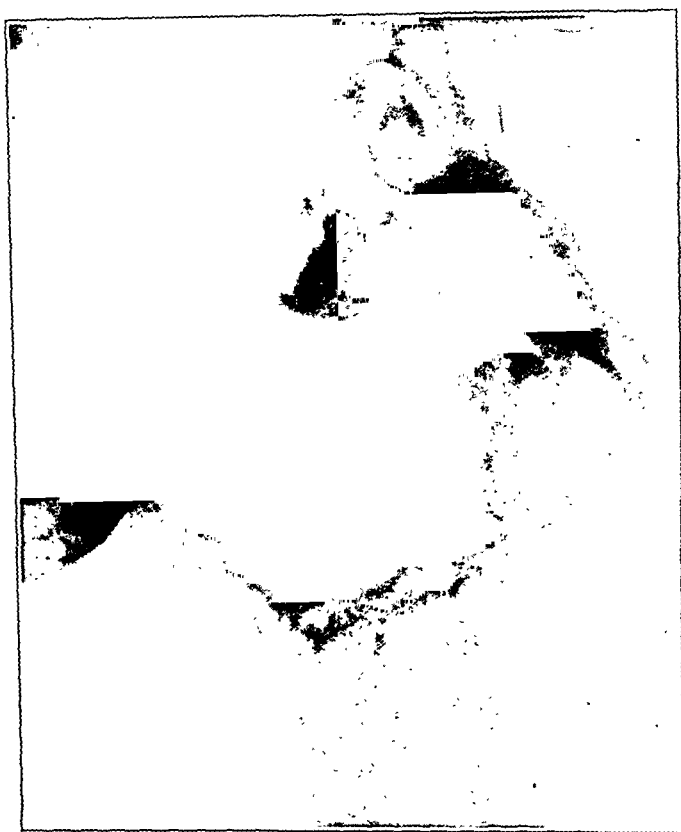


Fig. 5 (Path. no. 40810).—Roentgenogram of a dental root cyst of the mandible. This lesion is also polycystic and cannot be diagnosed from the x-ray film.

its periapical position about a nonvital tooth the apex of which may show evidences of erosion by the inflammatory process. When, however, the cyst becomes large so that its connection with a nonvital tooth can no longer be easily recognized, it is frequently impossible to rule out the less common jaw lesions. Figure 5 shows a polycystic lesion which at operation was found to contain granulation tissue and two cystic cavities filled with puslike material. This is a dental root cyst. Compare this with figure 4, a roentgenogram of an adamantinoma in the same jaw site. Both lesions are polycystic. Whenever a small cyst is found related to



a tooth, it is well to test the vitality of that tooth with a galvanic current. The finding of a vital tooth rules out the periapical root cyst.

The dentigerous cyst, a rare lesion arising from a cystic degeneration of the enamel organ, cannot always be diagnosed with certainty in the roentgenogram because of its contained tooth or tooth remnant, since adamantinoma in young persons, as well as giant cell tumor, which in the jaws has its highest incidence in patients under 20 years of age, may contain nonerupted teeth. In adults the adamantinoma has been known to override a molar tooth, producing a roentgen picture of a dentigerous cyst (fig. 6).



Fig. 6 (Path. no. 27596).—Roentgenogram of an adamantinoma situated at the angle of the mandible and expanding the walls of the ascending ramus so that the bone is not visible in the picture. Note the molar tooth that the tumor has overridden.

The giant cell tumor of the jaw shows a predilection for the angle and the symphysis of the mandible (Geschickter and Copeland<sup>13</sup>). In both positions its roentgen appearance, because of the trabeculation, may simulate a polycystic adamantinoma. A clinical diagnosis can usually be made because of the rapid rate of growth of the giant cell tumor. Seven months being the average duration of jaw cases. The rate of growth of the root cyst and the dentigerous cyst, however, is the same as that of the adamantinoma.

13. Geschickter, C. F., and Copeland, M. M.: Osteitis Fibrosa and Giant Cell Tumor, *Arch. Surg.* **19**:169 (Aug.) 1929.

Coincident with the swelling of the early tumor, which may not be noticed by the patient, the first symptom referable to the growth as found in histories of the cases presented is loose teeth. Since this is a very common symptom found in pyorrhea, dental caries, periostitis and other complaints, a careful investigation to rule out neoplasms was rarely made. Symptomatic treatment was given; the loose teeth were pulled. In fourteen cases a history of early extraction was found. Another frequent primary treatment was lancing, and in a few instances fluid was obtained. There is no doubt that if adequate roentgen studies had been made at the appearance of this early symptom of loose teeth, a cystic lesion would have been revealed the dissimilarity of which to the roentgen appearance of a small root cyst would have called for a diagnosis based on the examination of tissue.



Fig. 7 (Path. no. 23840).—Gross specimen of a solid adamantinoma which on section showed several small cysts.

In some instances it would appear that the extraction of the tooth accelerated the progress of the disease, because an increase in symptoms was noted after extraction. It is probable that following the trauma of extraction the epithelial elements are stimulated by the richened vascular supply, while the connective tissue is diverted to reparative rather than to epithelial reactive activities.

*Gross Pathology.*—The gross pathology of the adamantine epithelioma is characteristic. The tumor may be divided into two groups, the cystic and the solid. There is no sharp differentiation between these two, some tumors showing both a solid portion and cystic areas. On section some of these solid tumors, moreover, show cysts varying in size from minute almost microscopic structures to 1 cm. and more. Thirteen tumors were solid (fig. 7) and thirteen were cystic (fig. 8), while eight were described as having both solid and cystic areas. The solid areas

are composed of a cellular friable tissue, varying in color from grayish white to red hemorrhagic, lying in a fibrous stroma dividing the cheesy appearing epithelial areas into irregular islands. The glistening smooth-walled cysts are filled with a substance varying in consistency from a creamy to a watery fluid, and in color from grayish white to brown. Sometimes papillomas may be found projecting from the cyst wall. Some polycystic areas are similar in appearance to polycystic osteitis fibrosa. The solid primary tumors show a definite encapsulation so that they may sometimes be easily shelled out of their bony bed. There was one case in the laboratory in which a solid adamantinoma was mistaken



Fig. 8 (Path. no. 31404).—Gross specimen of a resected right lower jaw involved by a polycystic adamantinoma.

at operation for a giant cell tumor because of the granular and vascular tissue exposed, but usually the solid tumors are recognized at operation as epithelial.

The largest tumors are polycystic, and since most of the contents is fluid, the tumor can be immensely decreased by puncture (Lewis<sup>4</sup>). Fluid, however, soon returns. The small tumors of lengthy duration and the recurrent tumors are usually solid. The postoperative results show that the cystic lesions are more apt to recur than the solid growths.

*Microscopic Picture.*—There is no constant microscopic picture of the adamantinoma. The fundamental cell type is the basal cell, but all the degrees of differentiation of the enamel organ are found. Depending on this degree of differentiation, the tumor may be divided into two

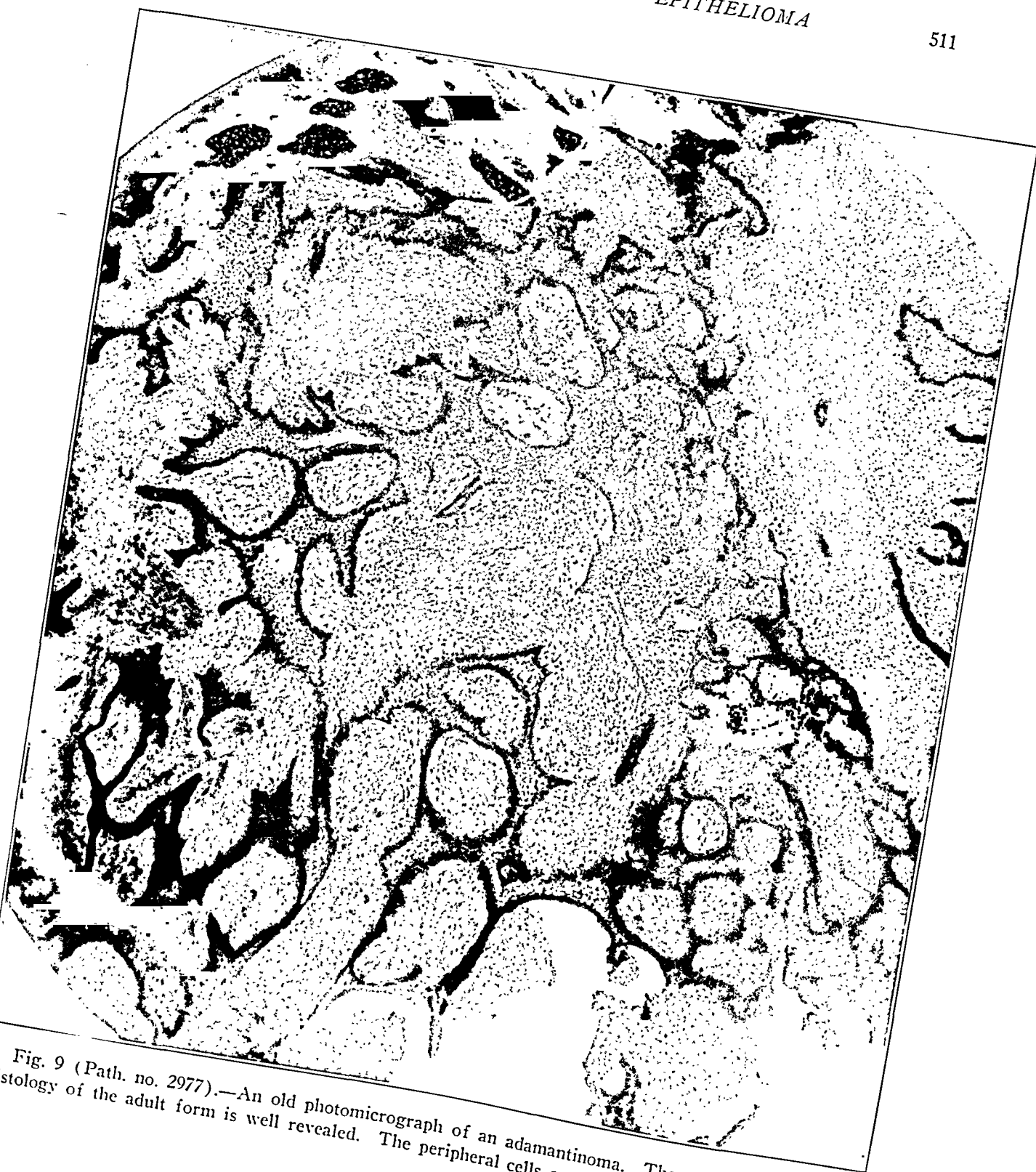


Fig. 9 (Path. no. 2977).—An old photomicrograph of an adamantinoma. The pattern of the gross histology of the adult form is well revealed. The peripheral cells are transitional.

groups, the adult (figs. 9, 10, 14, 15 and 16) and the undifferentiated forms (figs. 11 and 13). The adult form is most frequently seen. Lying in a stroma of widely varying cellularity are strands of epithelium

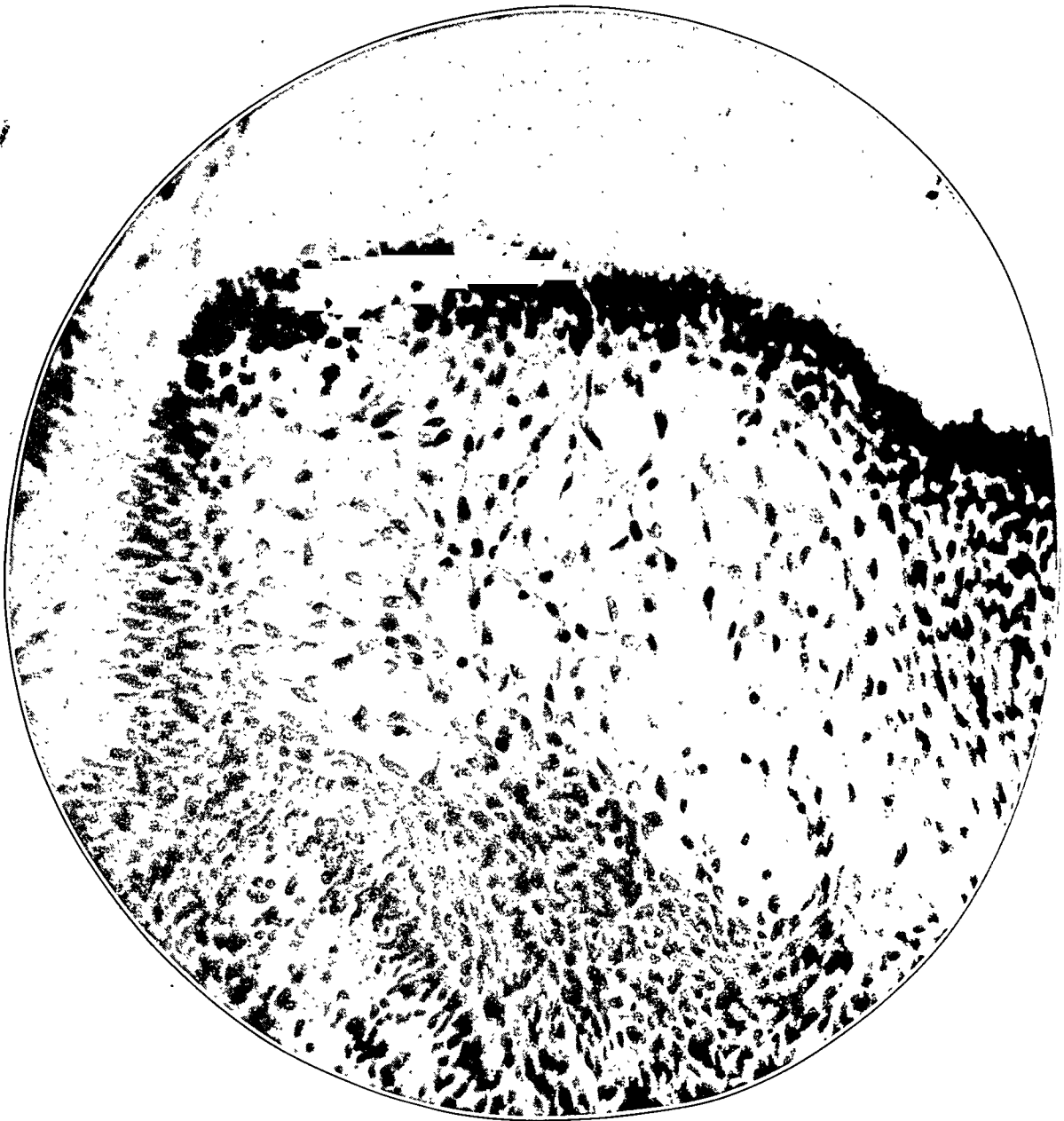


Fig. 10 (Path. no. 17524).—Photomicrograph of an adult adamantinoma. The stellate reticulum shows beginning cyst formation by an increase of intracellular fluid. Peripheral columnar cells and adjoining transitional cells can be distinguished.

sometimes very broad, sometimes quite thin, which branch out with multiple interconnections to form an epithelial network of fantastic configuration (fig. 9). The peripheral layer of cells, when cylindric,

is arranged in a palisade formation. The nuclei are situated basally, away from the limiting membrane, so that an area of less dense cytoplasm intervenes between the fibrous tissue and the cell nuclei (fig. 12). Next

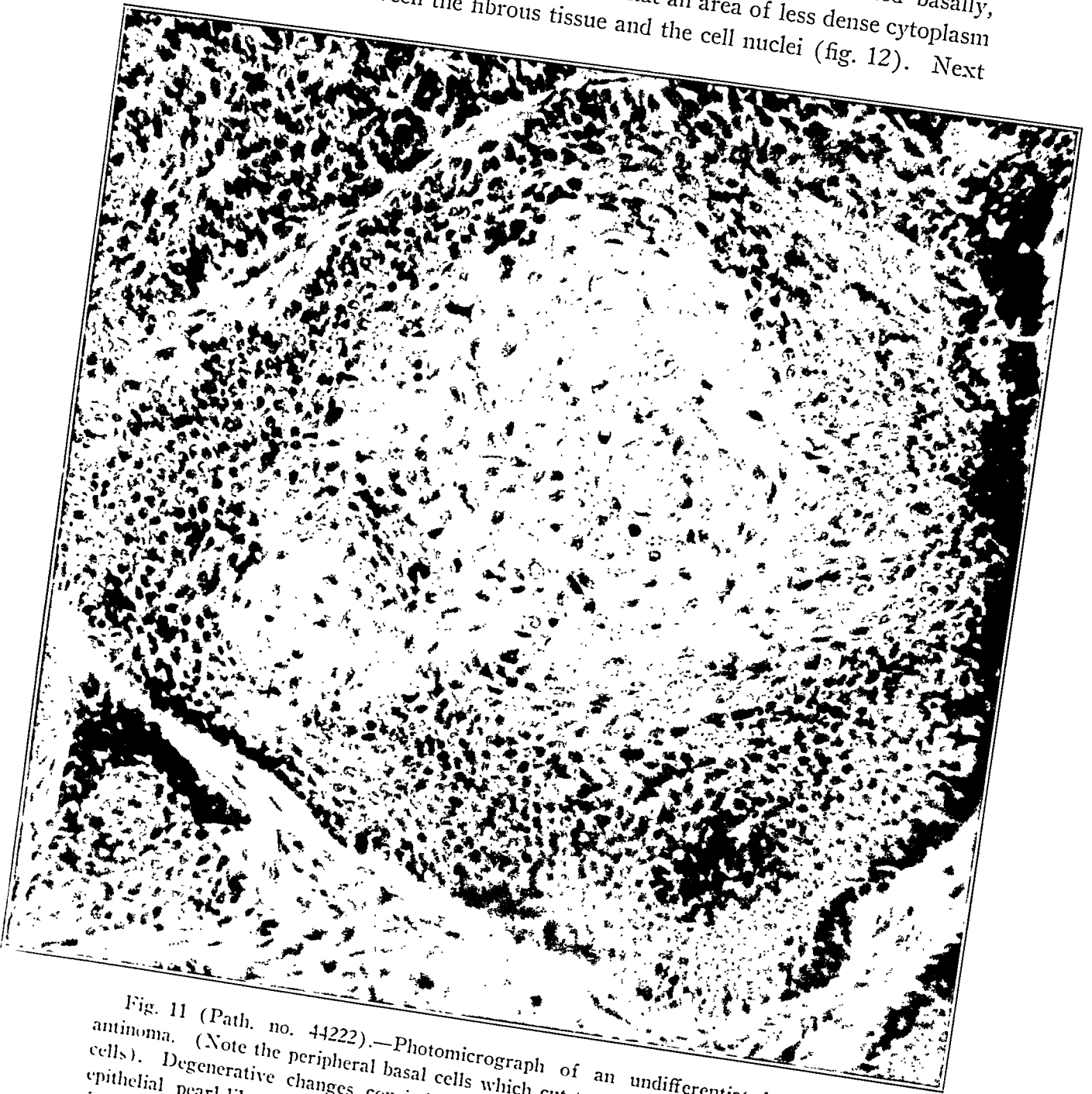


Fig. 11 (Path. no. 44222).—Photomicrograph of an undifferentiated adamantinoma. (Note the peripheral basal cells which cut transversely appear as round cells). Degenerative changes consisting in keratinization with the formation of epithelial pearl-like structures are to be seen in the center, a prelude to cyst formation.

to the peripheral layer lie the transitional cells, which merge into the stellate-shaped cells of the central portion of the epithelial strand (fig.

10). These stellate cells are less closely packed than the adjoining transitional cells. An increase of intercellular fluid pushes them apart so that the cytoplasm of contiguous cells is connected by thin fibrils.



Fig. 12 (Path. no. 42439).—Photomicrograph of a recurrent adamantinoma, showing a marked tendency to alveolar formation. The peripheral, tall columnar cells lie in palisade arrangement. The pseudocyst formation in the fibrous stroma is caused by mucoid degenerative changes. The basement membrane is closely adherent to the epithelial cells.

Frequently the peripheral layer, instead of being composed of cylindric cells, is made up of transitional cells of a morphology similar to the outermost cells of the enamel organ (fig. 9).



Fig. 13 (Path. no. 10834).—Photomicrograph of a solid adamantinoma in which cystic areas resembling adenoid cystic basal cell carcinoma are found together with cysts arising from epithelial degenerative changes.

In the less differentiated form, basal cells only are seen. These basal cells are arranged in solid clumps frequently of papillomatous conformation. In such forms there is no differentiation of the periph-



eral cells into columnar cells, although a palisade arrangement may be found. The outermost cells have oval, deeply stained nuclei of finely granular protoplasm. The cytoplasm is sparse, and the cells lie in a

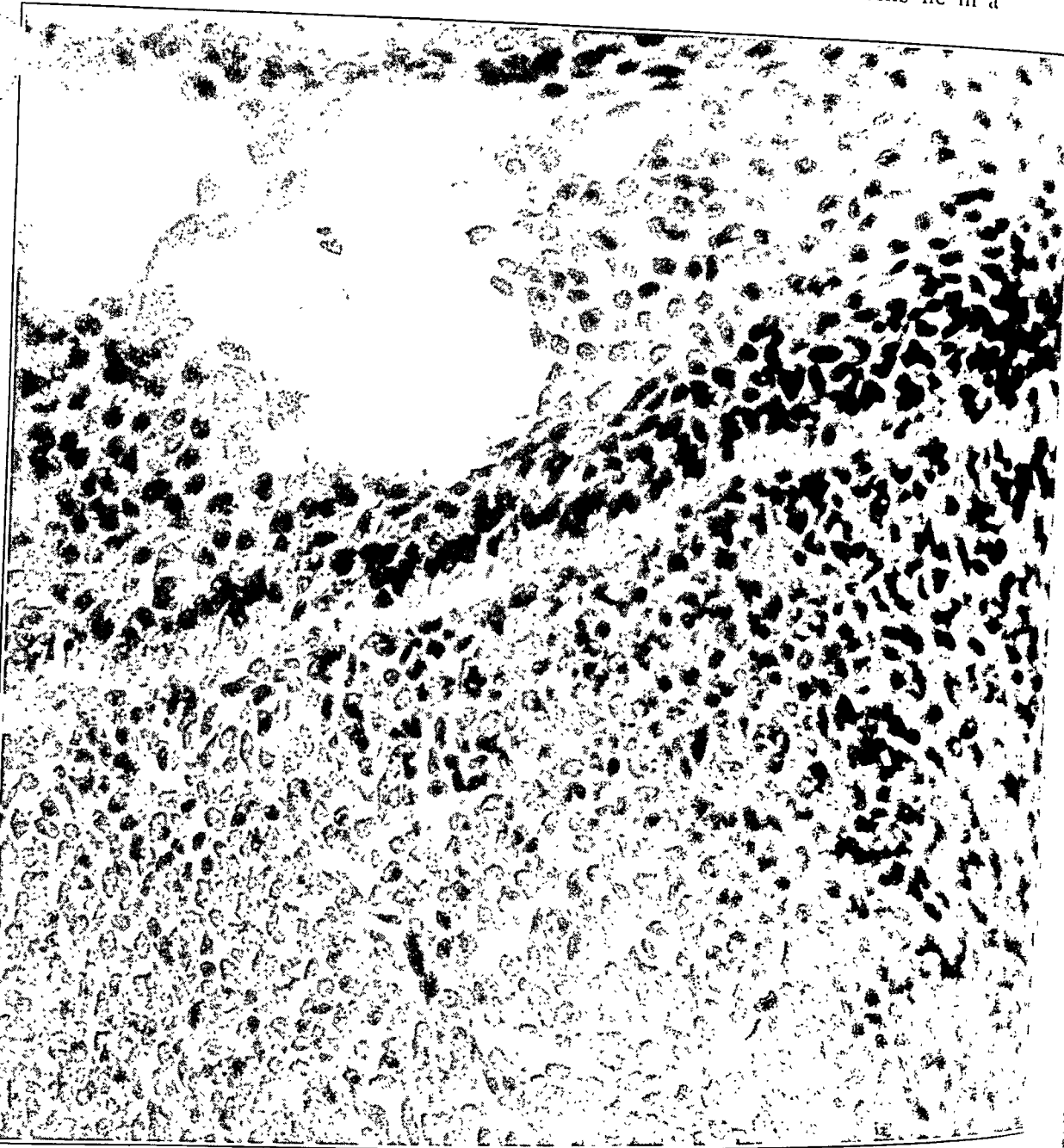


Fig. 14 (Path. no. 44954).—Photomicrograph of an adult adamantinoma in which the fibrous stroma (below) is composed of plump, oval fibrospindle cells. Note the mitoses marked by pyknotic figures. In the epithelium (above), cyst formation is seen. This is a so-called adamantinoma sarcomatodes.

delicate stroma. In cross-section the oval nucleus appears round so that in some areas the tumor resembles a spindle and round cell sarcoma.

In the central portion of these epithelial sprouts degenerative changes are frequently found, characterized by an increase in the amount of cytoplasm. Keratinization may take place; the cytoplasm becomes bloated; the nucleus becomes fainter and finally disappears (fig. 11).

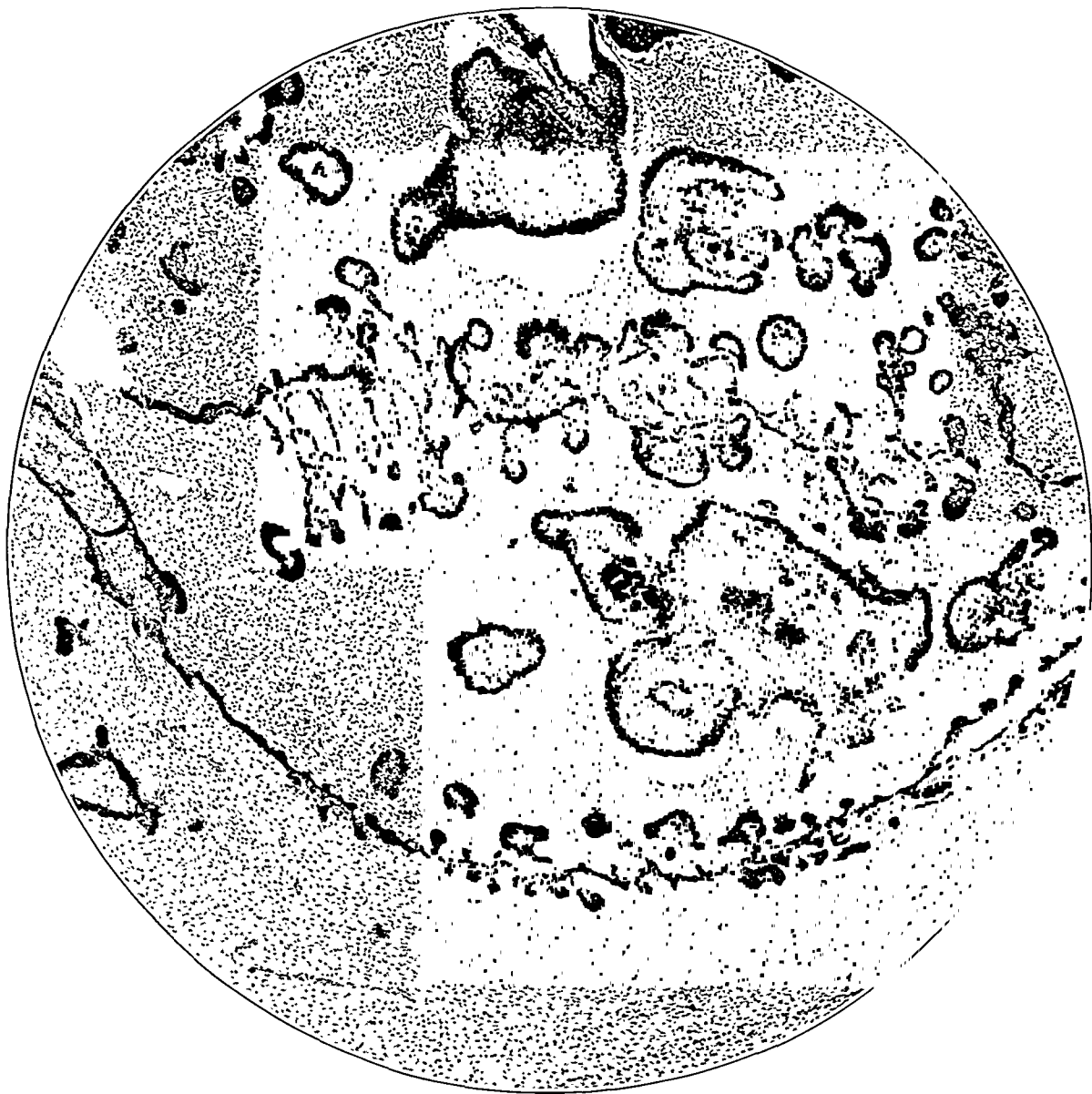


Fig. 15 (Path. no. 17527).—Photomicrograph of an adamantinoma with an embryonic stroma resembling primitive mesenchyme. The epithelial elements mimic the enamel organ. This is a so-called soft odontoma.

This series of changes is degenerative, and the basal cells show little tendency to differentiate into the cylindric transitional and stellate types of cells found in the mature form of the tumor.

When such an undifferentiated tumor occurs in the upper jaw, its cellularity may suggest carcinoma of the antrum. The following differences were noted in studying primary epidermoid carcinoma of the

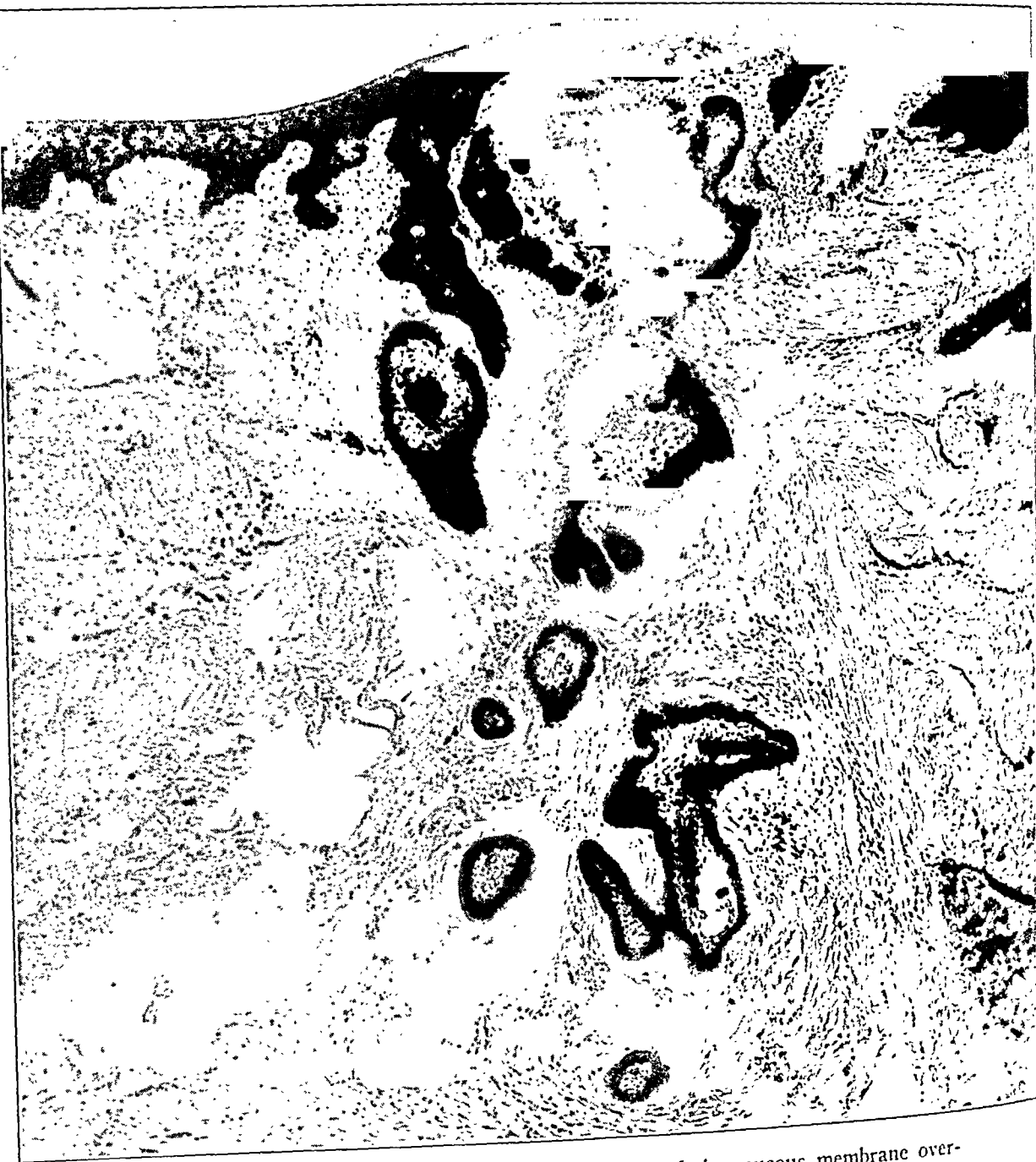


Fig. 16 (Path. no. 31404).—Photomicrograph of the mucous membrane overlying an adamantinoma. The secondary downgrowth of adamantine epithelium arising from the mucous membrane joins the tumor beneath.

antrum and adamantinoma: Microscopically, papillomatous epidermoid carcinoma of the antrum showed mitotic figures never noted in adamanti-

noma; the nuclei were hyperchromatic; pleomorphism was abundant. Clinically, the duration of the antrum tumors was much shorter than that of adamantinomas of the upper jaw, while the highest age incidence of antrum carcinoma was found after 50 years.

Between these two microscopic groups of differentiated and undifferentiated adamantinoma there are transitional forms. Then, too, a marked fibrous tissue reaction will disturb the epithelial morphology. Recurrences sometimes show marked anaplasia, as Ewing<sup>14</sup> pointed out. Figure 12 shows a recurrent tumor with a marked tendency to alveolar formation. The peripheral cylindric cells lie in a palisade arrangement.

Cystic formation is an almost constant microscopic observation. As has been pointed out by earlier investigators, this may take place by an increase in the intercellular fluids which push the cells apart so that they assume a star-shaped appearance and form a tissue recalling the stellate reticulum of the tooth germ (fig. 10). As the pressure increases, the cells are finally torn apart and disintegrate into globs of pink-staining material. A second form of cystic formation occurs by a degenerative change in the epithelial cell itself with little or no evidence of secretory activity (fig. 11). This degenerative change consists in cell keratinization with the formation of pearl-like structures which later liquefy to become cysts filled with a creamy thick fluid. Keratinization, but without pearl formation, is especially marked in infected tumors. Both kinds of cyst formation are seen in the adult form; the secretory type is rarely found in the undifferentiated form.

Pseudocyst formation occurs in the fibrous stroma by mucoid degenerative changes in the connective tissue elements (Derujinsky<sup>15</sup>). Such cystic areas may be lined by columnar epithelium, but the existence of an intact basement membrane speaks against the secretory activity of these cells (fig. 12). An atypical form of cyst was found in an undifferentiated adamantinoma (Path. no. 10834), while in other areas cysts arising by the usual degenerative changes were noted (fig. 13).

The lining of the large cysts varies from a stratified to a transitional type of epithelium which, when its morphology is altered owing to intracystic pressure, cannot be distinguished from that of the root and dentigerous cyst except when papillomatous outgrowths occur. These will show typical adamantine epithelium. This fact is of great importance, explaining the recurrent dental root cysts that prove to be adamantine epitheliomas at a second operation. What has happened is this: a monocystic adamantinoma is opened at operation; the cyst contents are

14. Ewing, J.: *Neoplastic Diseases*, Philadelphia, W. B. Saunders Company, 1928.

15. Derujinsky: Ueber einen epithelialen Tumor im Unterkiefer (Epithelioma adamantinum), *Wien. klin. Wchnschr.* 3:775, 1890.

emptied; the cyst lining is stripped from the cyst wall and is found to be transitional in type, while the strands of adamantine epithelioma deep in the fibrous wall or a solid portion of the tumor to one side are overlooked. After this incomplete removal, recurrence is inevitable.

The stroma of the adamantine epithelioma shows no constant morphology. Its quantitative proportion to the epithelial elements varies widely. At times the connective tissue is so reduced in amount that it forms small islands in large epithelial areas. The converse is also found. Usually the stroma is quite acellular, composed of cells with slender spindle-shaped nuclei. Reactive and regressive changes, mucoid and hyaline degeneration, cirrhosis and calcification are found. In some instances the fibrous reaction is as marked as that of a scirrhus carcinoma. The limiting membrane about the epithelium may be very dense. When the fibrous reaction is marked, cyst formation is more frequent.

In this series there are two adamantinomas to which, because of the distinctive characteristics of the connective tissue elements, continental observers have given special designations. In one case (Path. no. 44954, table 1), the stroma was of such cellularity that a differentiation of osteitis fibrosa and fibrosarcoma was difficult (fig. 14). The epithelium was of the differentiated form.

Papadimitriou,<sup>16</sup> who presented the fourth case of this kind to appear in the literature, suggested the name adamantinoma sarcomatodes. His case was characterized by a rapid growth (as is true of Path. no. 44954) and a duration of only eight weeks before operation. This author does not consider the fibrous element sarcomatous, but rather analogous to the stroma of the giant cell tumor and the giant cell epulis and hence clinically benign.

The second case with unique stroma characteristics is known in the German literature as the soft odontoma (Roemer). The fibrous stroma resembles primitive mesenchyme, being composed of cells of polygonal nuclei, fairly dense but with sparse cytoplasm and lying in reticular formation (fig. 15). The fibrous stroma is shot through by growths of epithelium of such morphology that the early downgrowth of oral epithelium is instantly recalled. Areas reproducing the conformation of the enamel organ are frequently seen. This tumor was locally malignant, and repeated curettage failed to check the later recurrences. The patient died from the tumor.

It is interesting to note that at the epithelial fibrous tissue junction, we have never observed the transformation of the stroma into odontoblasts. Whatever mimicry of the tooth germ occurs is shown by the epithelial elements alone.

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16. Papadimitriou, B.: *Zur Histologie und Histogenese der Adamantinoms.* Beitr. z. klin. Chir. **144**:556, 1928.

A careful study of the microscopic observations in relation to the duration and rapidity of growth and to the recurrences leads me to the conclusion that no grading according to malignancy or prognosis can be made. Among the tumors of a duration of ten years or more, microscopic areas were found identical with the typical areas from tumors of rapid growth and also from tumors of less than a year's duration. It was found, however, that a case in which there were repeated recurrences did show an atypical morphology. There is convincing evidence that primary recurrences are the result of improper treatment due to failure to use thermal or chemical cautery or to resect the jaw bone when indicated and not to a higher degree of malignancy. For among both the recurrent cases and the cases in which permanent cures have been obtained every type of histologic picture is represented. Simmons<sup>6</sup> reported two cases with glandular metastases, but there are none in this series.

*Microscopic Diagnosis.*—Under the microscope the differential diagnosis is important, because central jaw tumors frequently cannot be diagnosed from the history or from findings at examination. The large root cyst and follicular cyst and some dentigerous cysts are distinguished with certainty only at operation. The root cyst and follicular and dentigerous cyst show a lining of stratified squamous epithelium and so, too, do some monocystic adamantinomas. But in the fibrous tissue about the cyst wall of the latter and frequently in the epithelial lining of the cyst itself, areas of stellate basal cells will be found ruling out the benign growths. While studying cases with root and dentigerous cysts in this laboratory, four cases were found in which microscopic areas of adamantine epithelium were discovered. A microscopic diagnosis of adamantine epithelioma was made, and on looking up the case histories, the diagnosis was confirmed clinically because in all four of these cases the tumors were recurrent. Indeed, these were the only recurrences in the entire series of cases of dental root cysts and dentigerous cysts. It is for this reason that I believe that the so-called dentigerous cyst with a lining of adamantine epithelioma described by Scudder<sup>17</sup> and Bloodgood<sup>18</sup> is either not a clinical entity but a true adamantinoma, or else a root cyst the transitional epithelial lining of which has been described incorrectly as adamantine epithelium. The latter is the fact in a case reported by Barrie,<sup>19</sup> of which this laboratory has sections.

Giant cell tumor was the preoperative and operative diagnosis of an adamantinoma in two instances because of the red friable hemorrhagic

17. Scudder (footnote 8, p. 184).

18. Bloodgood, J. C., in Bryant, J. D., and Buck, A. H.: *American Practice of Surgery*, New York, William Wood & Company, 1909, vol. 6, p. 839.

19. Barrie, G.: Dentigerous Cyst of the Lower Jaw, *Ann. Surg.* **42**:352 (Sept.) 1905.

tissue found at operation. Central fibromas and fibrosarcomas, as well as chondromas, can usually be distinguished by the gross pathology at operation and always by the microscopic picture. The differential diagnosis of antrum tumors has already been discussed.

Carcinoma of low grade malignancy arising from the mucous membrane and secondarily infiltrating the jaw has sometimes been included among the adamantinomas. To this group the case described by Horsley<sup>20</sup> probably belongs. This patient (case 2, Mrs. A. R. T.) died of metastases to the lungs in December, 1931. The microscopic picture is atypical. In this laboratory there are three such cases with atypical histologic findings in which a careful history showed the mucous membrane of the gum or lip to be the course of the primary tumor. Squamous cell carcinoma of the mucous membranes secondarily invading the jaw and producing a cystic lesion can be recognized microscopically.

*Histogenesis.*—The origin of the adamantinoma is still in dispute. At present there are three main points of view: the tumor is held to spring from the paradental epithelial debris of Malassez, from the oral epithelium and from the enamel organ itself. Each of these theories will be discussed briefly.

The classic papers of Malassez pointed out the existence of certain epithelial remnants of the enamel organ, the paradental epithelial debris. In the development of the tooth, the epithelial, bell-shaped, enamel-producing portion of the tooth germ encapping a condensation of mesenchyme extends downward into the gum to the very apex of the future tooth. On completion of the enamel cap, this epithelium persists as an irregular cell strand extending down along the side of the tooth to the apical foramen, while over the occlusal surface of the tooth it persists as Hertwig's sheath. These groups of cells Malassez regarded as analogs of the rich dental apparatus of some of the lower vertebrates. Certain reptiles, for example, exhibit successive dentitions. To this paradental debris Malassez attributed the origin of root cysts, follicular or dentigerous cysts and adamantinoma. Bump<sup>21</sup> ably presented a similar view with excellent embryologic illustrations. There is no doubt that the paradental debris gives rise to the epithelium in the epithelial granulomas and root cysts. Dentigerous cysts, however, clearly arise by a cystic degeneration of the enamel organs, as is proved by the contained tooth remnant and a vacant space in the alveolus. No adamantinoma has been observed early enough, however, to prove the

20. Horsley, J. S.: Adamantine Epithelioma of the Lower Jaw, *Ann. Surg.* 79:358 (March) 1924.

21. Bump, W. S.: Adamantine Epithelioma, *Surg., Gynec. & Obst.* 41:173 (Feb.) 1927.

point of origin. As Perthes<sup>22</sup> remarked, the fact that root cysts, which undoubtedly arise from these remnants, never contain enamel or dentin while follicular cysts and adamantinomas do is proof that Malassez' epithelial rests have lost the power to form teeth or tooth remnants.

The oral epithelium has been suggested as a point of origin by some writers, among whom in this country is Broders, because of the discovery of a direct connection between the oral epithelium and the adamantine epithelium. But adamantine epithelium not infrequently comes in contact with the oral epithelium and sometimes invades it. In one case of the present series (Path. no. 31404) such a connection of oral epithelium and adamantine epithelium was observed (fig. 16). The history clearly shows, however, that this was a secondary downgrowth of the oral epithelium. The morphologic similarity common to all basal cell carcinomas, as witness the adamantinomas derived from the hypophyseal duct, is no proof of genetic relationship. Moreover, the age incidence of carcinoma of the gum is several decades later than that of the adamantine epithelioma.

The third view, that adamantinomas arise from the enamel organ, was advanced by Neumann<sup>23</sup> and Magitot.<sup>24</sup> The adamantine epithelioma arises by a neoplastic transformation of the tooth germ, while the follicular cyst and the dentigerous cyst result from a cystic degeneration of the same tissue. Broca<sup>1</sup> has clarified this concept by outlining three periods of tooth development: embryoblastic, odontoblastic and coronary. When cystic degeneration begins during the embryoblastic period in which only embryonic tissue and no hard substances are found, a follicular cyst is the result. Should this degeneration begin during the odontoblastic period during which the formation of dentin and enamel is in progress, that cyst will contain both dentin and enamel débris. During the coronary period in which the incidence of cysts is highest, cysts with tooth crowns or fully formed teeth are found. Cysts with tooth remnants or teeth are known as dentigerous cysts. Similarly, adamantinomas can be divided into three groups according to whether they contain merely embryologic elements, particles of dentin and cement or even small teeth. Adamantinomas of the last two groups are rare. All those of this series belong to the embryoblastic period. The odontoma is a solid tumor arising during the latter periods in which both enamel and dentin are found.

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22. Perthes: Ueber odontogene Kiefertumoren, München. med. Wchnschr. 52: 726, 1905.

23. Neumann, E.: Eine Unterkiefergeschwulst bedingt durch Degeneration eines Zahnsackes, Arch. f. klin. Chir. 9:221, 1868.

24. Magitot, E.: Mémoire sur les kystes des machoires, Arch. gén. de méd. 2:339, 1872.



The strongest evidence supporting the theory of Neumann and Magitot, which derives the adamantinoma from the germ bud, is a situation in which these tumors arise. The region of the molars is the one of predilection. Schlösser<sup>25</sup> found the ratio of the molars to other sites 79:14. In the upper jaw the molars and the lateral incisors are affected. Such a predilection for certain sites can be explained only by an origin from a tooth germ, for if the origin were from the mucous membrane or from the paradental debris of Malassez, there would be no constant distribution, since any area of the jaw might theoretically give rise to an adamantinoma.

There is both anthropologic and embryologic evidence that certain sites occasionally possess an excess of dental germ tissue. The angle of the jaw is the site of predilection for supernumerary molars, and the fourth molar is the most frequent of supernumerary teeth to appear. Zukerkandl,<sup>26</sup> who has studied the so-called epithelial rudiments of the fourth molar in man, found fourth molars more commonly in Negroes and other primitive races than among civilized peoples. In certain of the higher apes, notably the gorilla, the fourth molar is generally recognized. Zukerkandl considered the occurrence of a fourth molar an atavistic development. This evidence is sufficient to prove the existence of accessory tooth germs at the angle of the jaw. The strikingly high ratio of colored to white patients in the Johns Hopkins Hospital, 11:1, is in perfect agreement with the anthropologic data.

The upper jaw bears embryologic evidence in support of the tooth germ theory. In the development of the hard palate, three units are concerned, a central vomer and two lateral maxillae. The anlage of the lateral incisor tooth lies partly in the maxilla and partly in the vomer (Braus<sup>27</sup>). When the suture intra incisiva between the central nasal and the maxillary processes fails to unite, doubling of the lateral incisor occurs. Sometimes this reduplication is present with no other anomaly. In this site also, follicular and dentigerous cysts arise. This is evidence of supernumerary tooth germs and an explanation of the occurrence of adamantinoma in this site with secondary invasion of the antrum. The occasional finding of adamantine in other sites, such as the anterior portion of the lower jaw, can be explained by postulating the existence of supernumerary tooth germs. That these do exist is proved by the occasional appearance of a follicular or a dentigerous cyst in such an area.

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25. Schlösser, A.: Ueber einen Fall von Adamantinom, *Arch. f. klin. Chir.* **124**:679, 1923.

26. Zukerkandl, cited by Herbst, E., and Apffelstaedt, M.: *Malformations of the Jaws and Teeth*, London, Oxford University Press, 1930, p. 189.

27. Braus, Hermann: *Anatomie der Menschen*, Berlin, Julius Springer, 1924, vol. 2, p. 523.

In two cases of my series (Path. no. 38746 and Path. no. 40947, table 1) there was specific mention of the nonappearance of the third molars, at which site the tumor first arose. In the first case, the primary operation was done in this clinic, and no evidence of a third molar tooth was found at operation or in the gross specimen. The first symptom noted by the patient occurred at about the age of 16 years, when a swelling was noticed posterior to the second molar. This was lanced by a physician. A slight swelling remained in this region for seventeen years, after which an increase in size was noted. There can be no doubt that this adamantinoma arose not from a supernumerary tooth germ but from the third molar tooth bud which had undergone a neoplastic transformation that manifested few growth tendencies during a period of seventeen years. Unfortunately, cases in which such an origin from a tooth germ can clearly be demonstrated are few because the examiner and historian rarely note the number of teeth or question the patient as to the local point of origin. Furthermore, there are instances in which the patient himself is unable to localize accurately the site, having become aware of the growth only after it had extended over an area including several teeth.

Finally, the adamantinoma shows a marked predilection to arise during that age period in which eruption of the molar teeth takes place. The age group between 16 and 20 years showed the largest number of cases. This fact relates these tumors to the teeth and not to the mucous membrane of the gums, malignancy of which arises several decades later. The origin of a scattering of cases of adamantinoma at a later period can be explained in a few instances by the failure of the patients to recognize the growth in its incipency because of its extremely slow rate of growth. In other instances, it would seem that the dental germ underwent neoplastic transformation at a much later date. The cause of the neoplastic transformation has been variously ascribed to trauma, infection and mechanical irritation due to crowding.

*Treatment.*—The adamantinoma is par excellence a recurrent tumor. In nineteen of the thirty-five cases recurrences are known to have occurred. If the eleven cases in which primary radical resection was performed are excluded from the series, the percentage of recurrences following a conservative primary operation is raised to 79.

This series affords an opportunity to estimate the value of various operative procedures. A study of the ultimate results of treatment reveals that eleven patients were free from recurrences for five or more years; ten patients were well for less than five years and were then lost from observation, and five patients were free from recurrences for less than five years. Three patients died of the tumor and sepsis; there were three deaths after operation, and three patients were discharged from the hospital with tumors incompletely removed.

The operative attack used in the eleven cases in which the patients were free from recurrences for five or more years is shown in table 2.

A study of the operative attack used in the foregoing series indicates the need of radical intervention and the inefficacy of simple curettage. The most radical operation, resection of half of the jaw, is effective but mutilating. This operation was performed mainly in the early years of this hospital, when the tumors seen were huge and the preoperative diagnosis was carcinoma or sarcoma. A partial resection of the jaw was performed in three of the twelve cases, while a curettage followed by cautery was successful in three cases.

It will be noted that eight of the eleven were primary and three recurring tumors. Many of the recurrent tumors are not included in this group of cases in which cures were obtained, because the lesion was

TABLE 2.—*Operative Attack in Eleven Cases Free From Recurrence*

Path. No.	Operation	Operator	Freedom from Recurrence
566	Primary resection of lower jaw on left.....	Finney	11 years
2084	Primary resection of lower jaw on right.....	Halstead	5 years
2977	Primary partial excision of jaw and glands of neck.....	Cushing	5 years
4359	Resection of lower jaw following recurrence.....	Mitchell	21 years
7348	Curettage, chemical cautery.....	Sowers	9 years
10834	Partial excision of jaw with preservation of bony continuity .....	Churchman	17 years
27505	Resection of recurrent tumor, leaving bridge of bone; chemical and thermal cautery.....	Bloodgood	9 years
27596	Curettage of recurrent tumor; chemical and thermal cautery .....	Bloodgood	10 years
29750	Curettage; chemical cautery.....	Holman	8 years
31404	Resection of lower jaw following recurrence.....	Miller	8 years
33352	Radical operation on antrum; electric cautery.....	Crowe	7 years

first seen by the surgeon when small and easily treated. This paradox, that the tumors of long duration were successfully treated while tumors of short duration recurred repeatedly, is explained by the radical treatment accorded the former. Resection of the jaw bone was usually performed in the cases in which there were huge tumors. The small and therefore innocent-appearing lesion was usually lanced, incised or curetted on the assumption that it was a benign cyst. The recurrences were treated in the same manner until finally the local extension was too wide to be controlled.

The inefficacy of curettage alone was shown in two cases (Path. no. 14752 and Path. no. 17524), in which the primary treatment consisted of a series of repeated curettages followed by increasingly widespread local recurrences so that the patients finally died of the disease even after the most extensive operations and radiation therapy.

From a consideration of the operative results it would appear that when there is a monocystic or a solid lesion with an intact bone shell the operation of choice is curettage followed by chemical and thermal

cautery, as advocated by Bloodgood.<sup>28</sup> This procedure was effective even against a recurrent tumor, as instanced in one case (Path. no. 27596) in which there was a monocystic lesion. Bloodgood recommended removal of the tumor with a carbolic swab followed by alcohol and then a 50 per cent solution of zinc chloride. Thermal cautery follows. The expanded bone shell is resected subperiosteally. This treatment is successful against all the small cystic lesions that are so frequently met with in this age, whether the lesion is an adamantinoma, a dentigerous cyst, a giant cell tumor or a central fibroma. On the other hand, simple curettage alone will cure only the dentigerous and root cysts and rarely the giant cell tumor.

When the tumor is polycystic, so that curettage and cautery are unable to reach all the recesses to which the tumor may have extended, partial or total resection of the jaw bone is recommended. That it is not always advisable to preserve the continuity of the jaw by leaving a bridge of bone is indicated by Latenneur's<sup>29</sup> experience, who "in performing a resection left the lower portion of the mandible to act as a bridge between the resected ends. Eight years after, a cyst formed in this bridge. An attempt was made to destroy the growth with actual cautery, but the growth soon returned." When the tumor is in the upper jaw, Simmons<sup>6</sup> recommended resection of the maxilla. The defect in the hard palate may be closed with a plate.

As Bloodgood and others have noted, the recurrent tumor is more difficult to cure because of local extension and sometimes because of an actual increase in the rate of growth. The fact is clearly shown by the small number of recurrences of the cured group. They number less than a third of the five year group, while they constitute one half of the entire series. It is therefore important to note the number and type of previous operative interventions in all cases of adamantine epithelioma.

X-ray or radium has been tried in six instances, and in none of them has a beneficial result been noted. The adamantinoma is radio-resistant. In one case (Path. no. 14752), even the most skilful applications of radium resorted to after repeated recurrences failed to hinder the progress of the disease, which finally invaded the brain by local extension.

*Prognosis.*—The prognosis in persistently recurrent cases is not altogether dark, although it is hopeless as far as cure is concerned. The patient may experience several years without symptoms between recurrences. Five years is the average interval between the primary and secondary operations. Eleven years' freedom from recurrences was the longest interval noted in this series, although a longer period of

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28. Bloodgood, J. C.: Method of Operative Attack for Central Lesions of the Lower Jaw, New York State J. Med. 24:379 (March 21) 1924.

29. Latenneur, cited by Lewis (footnote 4).

forty-five years has been reported in the literature (Porzelt<sup>30</sup>). The eleven year period of freedom followed a resection of the lower jaw in a case in which repeated recurrences had not been checked by curettage. One patient (Path. no. 36927) is living and has a recurrence twenty-six years after her first symptom and about twenty-five years since the first of a series of operations extending to 1931.

Table 3 gives the duration of life in the cases in which death was known to have been caused by the tumor.

Death by direct extension through the base of the skull following a rupture of the bony wall with invasion of the soft tissues occurred in one case (Path. no. 38746). The primary operation was unavailing, being followed in eleven months by death.

TABLE 3.—*Duration of Life in Cases in Which Death Occurred*

Path No.	Age: First Symptom	Duration of Life After First Symptom	Duration of Life After Primary Operation
14752.....	19 years	29 years	28 years
17524.....	13 years	12 years	12 years
38746.....	19 years	17 years	11 months

#### CONCLUSIONS

1. The incidence of adamantine epithelioma is strikingly higher in Negroes than in white persons.

2. The findings on physical and roentgen examination establish the lesion as central; the diagnosis of adamantinoma depends on the gross and microscopic pathologic changes found at operation.

3. Microscopically, the adamantinoma is a basal cell tumor capable of reproducing all stages of the early enamel organ. The fully differentiated form is most often seen.

4. The presence of adamantine epithelium in the monocystic lesion is diagnostic of the adamantinoma and rules out the dentigerous and the root cyst.

5. The adamantinoma arises from the enamel organ.

6. The inadequacy of primary curettage in early cases is demonstrated by the high percentage of recurrences. After primary conservative treatment, there were 79 per cent of recurrences.

7. Curettage followed by chemical and thermal cautery, as advocated by Bloodgood under the conditions noted, is effective against all central jaw lesions.

The photomicrographs were taken by Mr. Herman Schapiro.

30. Porzelt, W.: Spaetrezidiv eines Adamantinome nach 45 Jahren. *Arch. f. klin. Chir.* **130**:142, 1924.

# HEAD INJURIES

## AN EXPERIMENTAL STUDY

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### HISTORICAL REVIEW

Severe head injury occasionally results in paroxysmal convulsive disorders which may be focal or general. Recently some clinics have come to use the aerogram to outline the brain cavities in order to visualize existent normality or deformity of these spaces. However, little is known at this time concerning the effects of head trauma on (1) the predisposition to convulsions and (2) the ventricular contour.

An attempt to measure experimentally these effects of head injury is presented.

Mention must be made of the work of others pertinent to this problem.<sup>1</sup> Brown-Séguard (1851), Nothnagel (1868), Westphal (1871) and Goltz (1892) were able to induce generalized convulsions in animals following a variety of head traumas. Concurrently, Magnam (1876), Victor Horsley (1885), Hughlings Jackson (1885) and recently Barbour and Abel (1910), Sauerback (1913), Syz (1923), Dandy and Elman<sup>2</sup> (1925), Pike and his associates<sup>3</sup> (1930) and Wortis<sup>4</sup> (1931) have shown by the use of various convulsant drugs and dyes, changes in an animal's susceptibility (to neurotoxic doses) following various cerebral manipulations.

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Accepted by the International Neurological Congress at Bern, Switzerland, Sept. 3, 1931, Section of Investigative Neurology.

From the Laboratory of Experimental Neurology, Department of Laboratories, Bellevue Hospital, Neurological Department (Cornell), Bellevue Hospital and Department of Neurology, University and Bellevue Hospital Medical College.

1. Dandy, W., and Elman, R.: Studies in Experimental Epilepsy, *Bull. Johns Hopkins Hosp.* **36**:1, 1925. Wortis, S. B.: Experimental Convulsions, *Am. J. Psychiat.* **11**:611 (Jan.) 1932.

2. Dandy and Elman (footnote 1).

3. Pike, F. H.; Elsberg, C. A.; McCulloch, W. S., and Chappell, M. N.: Some Observations on Experimentally Induced Convulsions, *Am. J. Psychiat.* **10**:567, 1931.

4. Wortis, S. B.: Head Injuries: Effects and Their Appraisal: 1. Experimental Studies of Induced Convulsions and Ventricular Distortion in the Cat, *Arch. Neurol. & Psychiat.* **27**:776 (April) 1932; *Proc. Am. Neurol. A.*, 1931, p. 348; footnote 1.

In histopathologic studies subsequent to brain injury, Cajal (1913), del Rio Hortega (1914), Foerster (1927), Bagley<sup>6</sup> (1928), Foerster and Penfield<sup>5</sup> (1930) and Stevenson and Wortis (1931) have attempted to show the rôle of the microglia in brain injury and repair.

Kennedy<sup>7</sup> (1931) recently described a plan for the evaluation of evidence in cases of head injury.

#### EXPERIMENTAL PROCEDURES AND FINDINGS

The cat was used as the experimental animal. To appraise the value of certain known injuries to the brain, this work was subdivided as follows: (1) the effects of brain laceration, (2) the effects of blood in the subarachnoid spaces and (3) the effects of skull fracture. Groups of animals were subjected to these procedures and subsequently given repeated injections of a standardized convulsant solution of camphor monobromide by a method previously described. The solution is made by dissolving 10 Gm. of camphor monobromide U. S. P. in 100 cc. of 95 per cent ethyl alcohol. Normal control animals require from 0.018 to 0.028 cc. of this solution intravenously per pound to induce generalized clonic and tonic convulsions. It is our experience that injections of camphor to produce convulsions, repeated at intervals of several days, over a period of four months, do not affect the minimal convulsant dose—an observation also made by other workers.<sup>8</sup>

*Brain Laceration.*—In one group of fifteen animals aseptic brain lacerations of various cerebral areas were produced. Under ether anesthesia, the hair over the skull was clipped and then entirely removed by depilatory. The skin area was washed with sterile soap and water and painted with 5 per cent tincture of iodine. The scalp was incised in the midline, the temporal muscle was retracted, and a small bit of bone removed by trephine. The dura was then punctured with a needle or knife, and the underlying cortex was traumatized (but not removed) to a depth of 2 mm., over a surface area of from 2 to 3 sq. mm. In some instances a needle puncture of the brain was done, the products of trauma being left in situ. The overlying muscle and skin were sutured back in place, black silk being used.

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5. Foerster, O., and Penfield, W.: The Structural Basis of Traumatic Epilepsy, *Brain* **53**:99, 1930.

6. Bagley, Charles: Functional and Organic Alterations Following the Introduction of Blood into the Cerebrospinal Fluid, *Proc. A. Research Nerv. & Ment. Dis.* **8**:217, 1928.

7. Kennedy, Foster: Head Injuries: Effects and Their Appraisal: I. Evaluation of Evidence, *Arch. Neurol. & Psychiat.* **27**:811 (April) 1932.

8. Davidoff, L., and Kopeloff, N.: Repeated Experimental Convulsive Seizures in Rabbits, *Proc. A. Research Nerv. & Ment. Dis.* **7**:183, 1929.

The findings in this group of experimental animals have been in part reported elsewhere.<sup>9</sup> It is sufficient at this time to reproduce the results of repeated injections of camphor (table 1).

Increased sensitiveness to a standardized convulsant was noted in addition to the gross histopathologic findings of: (1) meningo-cerebral adhesions, (2) contracting cerebral cicatrix and (3) ventricular distortion (which will later be discussed in greater detail).

*The Effects of Blood in the Subarachnoid Spaces.*—A group of six animals was operated on aseptically by the following method. The

TABLE 1.—*Experimental Results in Fifteen Animals*

	Number of Animals	Cc. of Standardized Convulsant per Pound of Cat		
		1 Day After Injury	4 Days After Injury	10 Days After Injury
Left motor cortex.....	5	0.024	0.024	0.018
Left parieto-occipital cortex..	5	0.022	0.022	0.020
Left cerebellar cortex.....	5	0.022	0.022	0.020

TABLE 2.—*Effect of Blood in the Subarachnoid Spaces in Six Animals \**

Pupils:	
Equal .....	2
L > R.....	4
Palsies: Only transient palsies of right limb present for from 2 to 3 hours after operation	
Convulsions induced with camphor at following time periods after operation: 97 minutes and 2, 6, 8 (2), 9, 13, 14, 15, 18, 24, 32, 33, 41, 60, 72, 84, 89, 102 and 135 days	
Animals killed or died: 6, 20+, 33, 84, 102, 135 days	
Brain:	
Congestion .....	1
Meningocerebral adhesions .....	4
Normal .....	2
Ventricular system normal.....	6
Meninges:	
Thickening (or adhesion).....	5
Normal .....	1

\* Each animal received 0.5 cc. of its own blood into subarachnoid space over the left parietal region.

surgical approach was the same as that recorded for the series in which brain lacerations were produced. After removal of the "bone button" by trephine, 0.5 cc. of the animal's own blood (obtained from a femoral or scalp vein) was introduced with a minimal amount of trauma (by means of a very fine hypodermic needle and syringe) into the subarachnoid space over the left parieto-occipital regions. The muscles, fascia and skin were closed over in the usual manner. At varying postoperative periods convulsions were produced by the use of the standardized solution of camphor. The results are shown in tables 2 and 3.

9. Wortis (footnote 1).



*Skull Fracture.*—Twenty-four animals were subjected to skull fracture by striking the animal suddenly with a 1 pound hammer over the left frontoparietal skull area. The cat would suddenly become limp; many lost consciousness, and in a few, respiration ceased momentarily.

TABLE 3.—Data on Animals with Subarachnoid Hemorrhages

No. of Ani-	Date of Operation	Neurologic Signs	Convulsant		Postmortem Results
			Convulsions After Operation	Dose, Cc. per Pound of Animal	
61	2/10/31	Left pupil > right	6 days right > left	0.018	Animal killed sixth day after operation; slight congestion over left cortex; slight meningeal adhesions to cortex over left parieto-occipital region; ventricular system normal; slight amount of blood in first, second and third ventricles
64	2/10/31	Left pupil > right; weakness of right fore and hind limb	Head to right 8 days; clonic beginning on right side	0.013	Cat died twentieth day after operation; pneumonia; dura adherent to region about trephine; osteomeningocerebral adhesion to outer portion of left cruciate sulcus; ventricular system normal
			13th day	0.013	
90	4/ 2/31	Normal; pupils equal	33 days; on manipulation went into convulsion spontaneously; possibility of having used cocaine as local anesthesia; animal died in status	.....	Animal died 23 days after operation; meningocerebral adhesion to muscle fascia covering the trephine hole; dura on left thick and opaque; ventricular system normal
92	2/10/31 Very light ether and local for skin	Head torsion to right side; left pupil > right	97 min.	0.023	Animal killed 102 days after operation; meningocerebral adhesion to point just behind left motor cortex; dura is slightly thickened; ventricular system normal
			8 days slight scalp infection drained; no stiff neck		
			9 days convulsion more marked on right side	0.018	
			14 days "running nose"		
			89 days	0.012	
98	4/ 2/31	Symmetrical convulsions; pupils equal	102 days	0.015	Animal killed 84 days after operation; trephine hole almost closed in by scar tissue; no meningocerebral adhesions; brain grossly normal; ventricular system normal
			32 days	0.015	
			41 days	0.015	
			60 days	0.012	
			72 days	0.015	
99	2/10/31	Left pupil > right; head drawn right side	84 days	0.015	Animal killed 135 days after operation; slight thickening and opaqueness of the left dura; no meningocerebral adhesions; brain grossly normal; ventricular system normal
			2 days		
			15 days slight infection right eye		
			15 days	0.015	
			18 days	0.010	
			24 days	0.013	
			91 days	0.012	
			135 days	0.012	

This series also had a definitely increased susceptibility to camphor following head trauma. Some associated ventricular distortion and meningeal hypertrophy or adhesions are recorded. The results are shown in tables 4 and 5.

After varying periods had elapsed, the animals were killed, a solution of bromoformol  $[(CH_2)_6N_4C_2H_5Br]$  was injected into the arterial system via the heart, the viscera were examined, and the brain was

removed and placed in the same fixative. From seven to ten days later the brain was examined, grossly sectioned and all abnormal changes noted. Some of the specimens were photographed, and finally all were embedded in celloidin, sectioned, and stained with hematoxylin and eosin or by the Loyez method.

Control groups of intact animals were subjected to convulsions at similar time intervals, and their viscera treated in the same manner.

#### SOME OBSERVATIONS ON ASSOCIATED EXPERIMENTALLY INDUCED CONVULSIONS AND VENTRICULAR DISTORTION

Brain laceration, blood in the subarachnoid spaces and skull fracture (which causes one or both of the previously named conditions) cause

TABLE 4.—*Effect of Skull Fracture in Twenty-Four Animals*

Findings at time of injury:		Gross postmortem findings in 24 specimens:	
Unconsciousness .....	18	Brain—Continued:	
Bleeding from orifices.....	17	Blood in ventricular system (one	
Convulsions (tonic, extension or		marked hematocephalus) .....	4
clonic) .....	11	Normal .....	8
Paralysis (right-sided) .....	11	Meninges:	
Skull deformity discernible.....	3	Thickened or adhesions.....	8
Pupils:		Normal .....	16
Equal or moderately dilated.....	14	Ventricles:	
R > L .....	2	Slight to moderate general dilata-	
L > R .....	8	tion (bilateral) .....	8
Loss of sphincter control (bladder or		Left lateral ventricle dilated.....	1
bowel) .....	7	Hematocephalus .....	1
Gross postmortem findings in 24 specimens:		Slight amount of blood in ventricles	3
Skull fracture:		Normal .....	11
Linear .....	5	Time distribution of specimens:	
Depressed .....	2	Died directly following trauma.....	4
Grossly normal (macroscopic exam.).	17	Killed after convulsions (camphor in-	
Brain:		jections) .....	20
Gross laceration .....	2	Distribution: 113 minutes and 6, 9, 17,	
Hemorrhage into brain or over cor-		23, 35, 44, 50 (2), 55, 56 (2), 68, 72, 93,	
tex .....	6	102, 104, 129 and 151 days	
Adhesions (meningocerebral) .....	7		

the cat to be abnormally sensitive to a solution of monobromated camphor used to induce generalized convulsive seizures. This increased susceptibility to camphor usually can be demonstrated four days after injury and in most of the animals studied can be shown to persist over a period of at least from three to four months. After this time, some of the animals may require the same quantities of camphor to produce generalized convulsions as are necessary for intact control animals. These findings are probably related to physicochemical (and in some instances visibly histopathologic) changes in the brain and its coverings. Bagley demonstrated in puppies subjected to repeated injections of blood by the cistern route the occurrence of spontaneous convulsions associated with meningeal changes. Our series also shows the occurrence of meningeal thickenings and adhesions. In cases of long standing with markedly thickened meninges and meningocerebral adhesions, degenerative cellular changes occur in the underlying cortex. This brings to mind the clinical group of postmeningitic epilepsies, and suggests surgical measures as a means of mitigation in cases in

TABLE 5.—Data on Animals With Skull Fracture

Evidence of Fracture at Injury				Convulsions Produced by Camphor				Postmortem Results
Unconscious	Bleeding	Sphincter Control	Paresis	Reflex Pupil Changes	Time After Injury	Weight, Pounds	Dose per Pounds, Oe.	
Yes	Mouth	Clonic	.....	L > R; dilatation	.....	...	.....	.....
50	Yes	Clonic	.....	L > R; dilatation	.....	...	.....	Cat died 4 min. after injury; linear fracture of left parietal bone through base; dura intact; blood around base and in ventricular system
54	Yes	Clonic	.....	Dilatation	.....	...	.....	Cat died 10 min. after injury; skull intact; blood all over cortex and base; ventricle normal in shape with slight amount of blood
54A	Yes	Clonic and tonic	Defecation	L > R	6 days 23 days	7 6¼	0.018 0.015	Died 23 min. after injury and injection of camphor; fissure fracture of left parietal bone; thickening of pia, with attachment to skull and brain at fracture site; slight ventricular dilatation
55	Yes	Clonic; "back flips"	.....	.....	.....	...	.....	Died 8 min. after injury; depression fracture, left frontoparietal region, 2 cm. in diameter; blood over brain and around base; clot in left ventricle (hematocephalus)
56	Yes	Clonic	Urination	Dilatation; spastic gait	113 min.	8	0.028	Died 145 min. after injury and injection of camphor; skull intact; blood all over cortex; slight amount of blood in right ventricle
57	Yes	Clonic and tonic	..... Right hemisphere, especially fore paw	Dilated; equal	16 days	7	0.028	Died 17 days after injury and injection of camphor; skull intact; attachment of pia to skull and brain over left posterior temporo-occipital cortex; blood in left frontal sinus; old blood over entire cortex; ventricle system, slight dilatation; no distortion; pneumonia
59	Yes	Tail bushing	.....	Dilated	.....	...	.....	Died 9 days after injury; skull intact; dura slightly thickened; slight internal hydrocephalus; sinuses with pus; pneumonia; blood over cortex
60	Yes	Mouth Tonic; respiratory failure (artificial respiration)	Defecation	Head retracted	1 day 2 days	6 6	0.024 0.020	Died 6 days after injury; depression fracture 2 cm. in diameter; hemorrhage in left frontal sinus; brain laceration and blood over left motor cortex; ventricular system, slight dilatation and pushed toward right

65	Yes	.....	.....	.....	L > R	10 days 21 days 34 days	7 6½ 6%	0.015 0.013 0.013-0.015 defective injection	Clonic Clonic Clonic	.....	Died 50 days after injury; skull intact; brain appears normal; meninges normal; ventricular system normal
66	....	Nose	.....	.....	Equal	41 days 50 days	6 6%	0.012 0.012	Clonic Clonic	.....	Died 56 days after injury; skull intact; dura adherent to brain, left parietal region; ventricular system normal; pneumonia; septic liver and spleen; infection of left frontal sinus
69	Yes	Mouth	.....	Defecation	Right fore limb	18 days 29 days 47 days	8 7 6%	0.025 0.018 0.012	Clonic Clonic Clonic	Respiratory infection, febrile; pneumonia	Died 35 days after injury; skull intact; brain grossly normal; slight bilateral ventricular enlargement, especially right inferior horn
70	....	.....	.....	.....	Right hemi-sphere	6 days 15 days 44 days	6 6½ 7	0.015 0.014 0.014	Clonic Clonic Clonic	.....	Died 44 days after injury; skull intact; dura thickened, no attachment; ventricular system normal
71	Yes	.....	Tail bushing	Urination	Right hemi-sphere	2 days 55 days	7 9½	0.020 0.014	Clonic Clonic	.....	Died 55 days after injury; linear fracture of left frontal bone into left frontal fossa; brain and dura adherent at this point; slight internal hydrocephalus
72	....	Mouth	Tail bushing	.....	Marked ataxia	27 days 33 days 42 days 50 days	7 6½ 6½ 6½	0.018 0.018 0.018 0.015	Clonic Clonic Clonic Clonic, head torsion to right	.....	Died 72 days after injury; skull intact; meninges slightly thickened; brain normal; ventricular system normal
73	Yes	Mouth and nose	.....	.....	.....	8 days 16 days 50 days	6½ 6 7%	0.014 0.013 0.012	Clonic Clonic Clonic	.....	Died 50 days after injury; skull intact; dura thickened, adherent to parietal skull and brain; ventricular system normal
74	....	Mouth	.....	.....	Right hemi-sphere	14 days 20 days 30 days 41 days 68 days	5 5½ 6½ 7½ 6%	0.013 0.013 0.012 0.011 0.016	Clonic Clonic Clonic Clonic Clonic	.....	Died 68 days after injury; skull intact; dura slightly thickened; brain normal; ventricular system normal; spleen enlarged
76	Yes	Mouth	Clonic; tail bushing; tonic extension	Defecation	.....	.....	...	.....	.....	Slightly febrile	Died 5 min. after injury; depression fracture, midline; lacerated brain cortex, both sides; blood all over brain; blood in ventricular system

TABLE 5.—Data on Animals With Skull Fracture—Continued

Evidence of Fracture at Injury				Convulsions Produced by Camphor			Complication	Postmortem Results	
Unconscious	Bleeding	Convulsion	Sphincter Control	Paresis	Reflex Pupil Changes	Time After Injury			Dose per Weight, Pound, Pounds
S0	Yes	Mouth	.....	Right fore paw	Equal; dilated	13 days 24 days 36 days	5 5½ 5½	Clonic Clonic Clonic and slightly tonic	.....  Died 120 days after injury; brain grossly normal; ventricular system normal; no adhesions
						44 days 94 days 120 days	5¾ 5½ 5½	Clonic Clonic .....	Diarrhea
E1	Yes	Nose	"Back flips"	.....	L > R	12 days 19 days 67 days 151 days	9 9½ 10 10	Clonic Clonic Clonic Clonic	.....  Died 151 days after injury; no outward gross brain lesion; left lateral ventricle slightly dilated
E2	Yes	Nose	Tonic extension; head torsion to right	Right hemisphere	Dilated	21 days 56 days	6½ 7¼	Clonic Clonic	.....  Killed 56 days after injury; no bone fracture seen; slightly adherent dura about left cruri-ate gyrus; ventricular system slightly dilated bilaterally
S3	....	Mouth	Tail bushing	.....	R > L	23 days 104 days	6 6	Clonic Clonic	.....  Killed 104 days after injury; no bony fracture; no dural adhesions; ventricular system normal
S1	Yes	Mouth	Tonic extension	.....	.....	40 days 102 days	6½ 6½	Clonic Clonic	.....  Killed 102 days after injury; no bony fracture no dural adhesions; ventricular system normal
S5	Yes	Mouth	Tonic extension	Defecation	Right fore paw	38 min. 11 days 94 days	5½ 9 9	Clonic Clonic Clonic	.....  Killed 94 days after injury; no bony fracture made out; moderate bilateral internal hydrocephalus; no adhesions seen
S6	....	Mouth	.....	Right hemisphere	.....	31 min. 13 days 93 days	5¾ 5 5	Clonic Clonic Clonic	.....  Killed 93 days after injury; no evidence of bone fracture; no adhesions; ventricular system is normal

which the condition is refractory to intensive sedative, acidotic and dehydrational medication, and is not helped by air encephalography which reveals cortical adhesions.

Brain laceration gives rise to meningocerebral adhesions and contracting cerebral cicatrix. Foerster and Penfield demonstrated this experimentally and devised a surgical method for stopping convulsive phenomena dependent on this pathologic process of the brain.



Fig. 1.—Low power photomicrograph of a section of the brain of a cat twenty-five hours after injury. The brain puncture wound filled with a blood clot. The microglia cells in the contiguous area began to swell in a very short while.

#### SOME ASSOCIATED HISTOPATHOLOGIC CHANGES

The tissue changes associated with brain laceration and repair have been described by Virchow (1846), Robertson (1897), Cajal (1930) and Stevenson<sup>10</sup> (1931). The rôle of the microglia in brain repair has

10. Stevenson, L. D.: Head Injuries: Effects and Their Appraisal: II. The Rôle of the Microglia, *Arch. Neurol. & Psychiat.* 27:784 (April) 1932; *Proc. Am. Neurol. A.*, 1931, p. 356.

been stressed by most of these investigators. The microglia cells are found throughout the nervous system, especially surrounding nerve cells and small blood vessels, to which vessel walls the microglia cell processes do not attach. The cell has a small or elongated nucleus, and the cytoplasm is granular and often fusiform. Whether the origin of the microglia is mesodermal (as believed by del Rio Hortega and Marinesco) or ectodermal (Roussy, Lhermitte, Oberling) is not germane to this study.

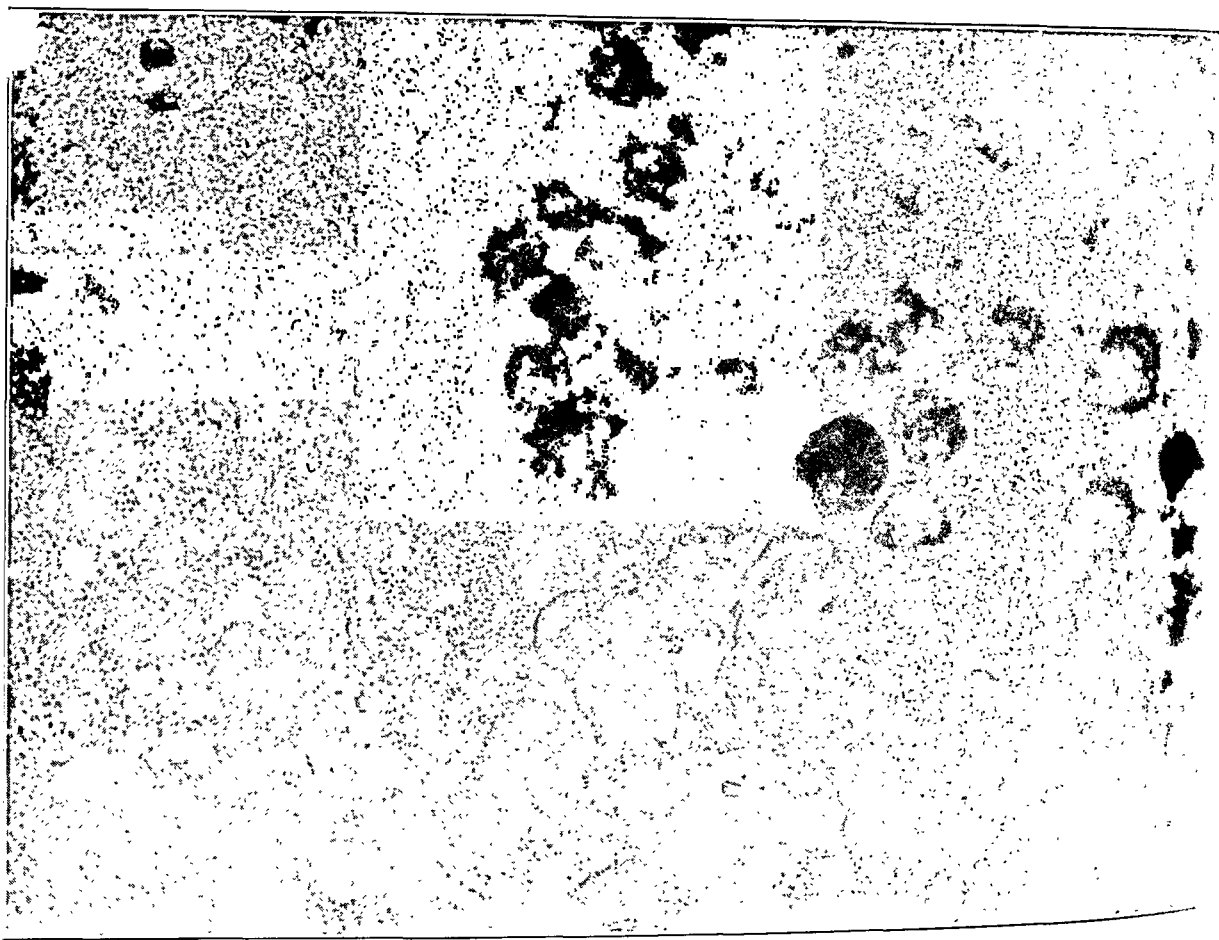


Fig. 2.—High dry power photomicrograph of a section of the brain of a cat ninety-five hours after injury. The microglia cells in the region of the wound have been transformed into compound granular corpuscles (*Gitterzell*). They contain slight amounts of fat and iron pigment. There is also swelling of the astrocytes in this area.

The neuroglia is made up of the following:

- (1) Macroglia (a) protoplasmic astrocytes—found especially in gray matter.  
(b) Fibrillary astrocytes—found especially in white matter, usually attached to blood vessel sheath by “foot.”
- (2) Oligodendroglia—found in gray and white matter.
- (3) Microglia—found throughout nervous system.

It is only in the latest stages of embryonic development that the microglia becomes visible. According to del Rio Hortega, the two principal sources are: the superior choroidal membrane and the pia covering the cerebral peduncles and, down lower, in the inferior choroidal membrane and in the spinal meninges.

All brain injuries resulting in destruction of brain tissue (and especially where the products of trauma remain in situ) are followed by mobilization and changes in the surrounding microglial elements.

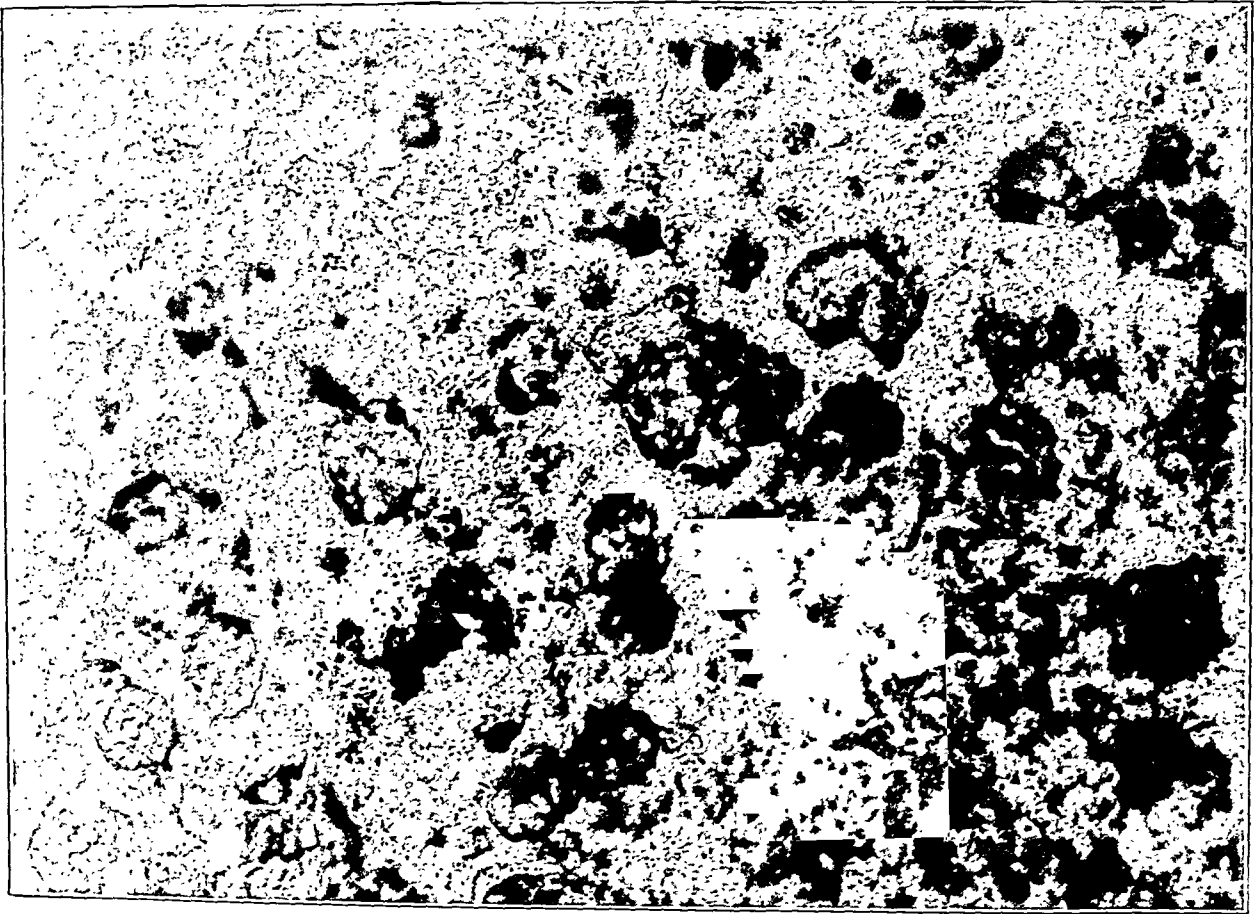


Fig. 3.—High dry power photomicrograph of a section of the brain of a cat seven days after injury. Compound granular corpuscles are seen.

Early the cell processes are swollen and retracted and begin their phagocytic activities, at which time they are transformed into the compound granular cell form. By this agent, the destroyed cerebral elements are removed, and subsequently with the microglia still in predominance, cicatricial gliosis begins. The other cellular elements also participate in brain repair, and some believe that the oligodendroglia and to a lesser degree the astrocytes participate in the phagocytic process. Related neuroglia astrocytes (i. e., those not destroyed by



the original trauma) undergo multiplication and enlargement and become fibrous, and finally cicatricial contraction of the scar results with secondary brain tissue deformity. Most often the microglial elements are overzealous in their phagocytic activities, and probably injure or destroy neighborhood cerebral tissue.

Thus simple brain laceration may result in: (1) destruction of brain cellular elements (sometimes in excess of that attributable to the initial injury), (2) brain scarring with or without related meningeal adhesions

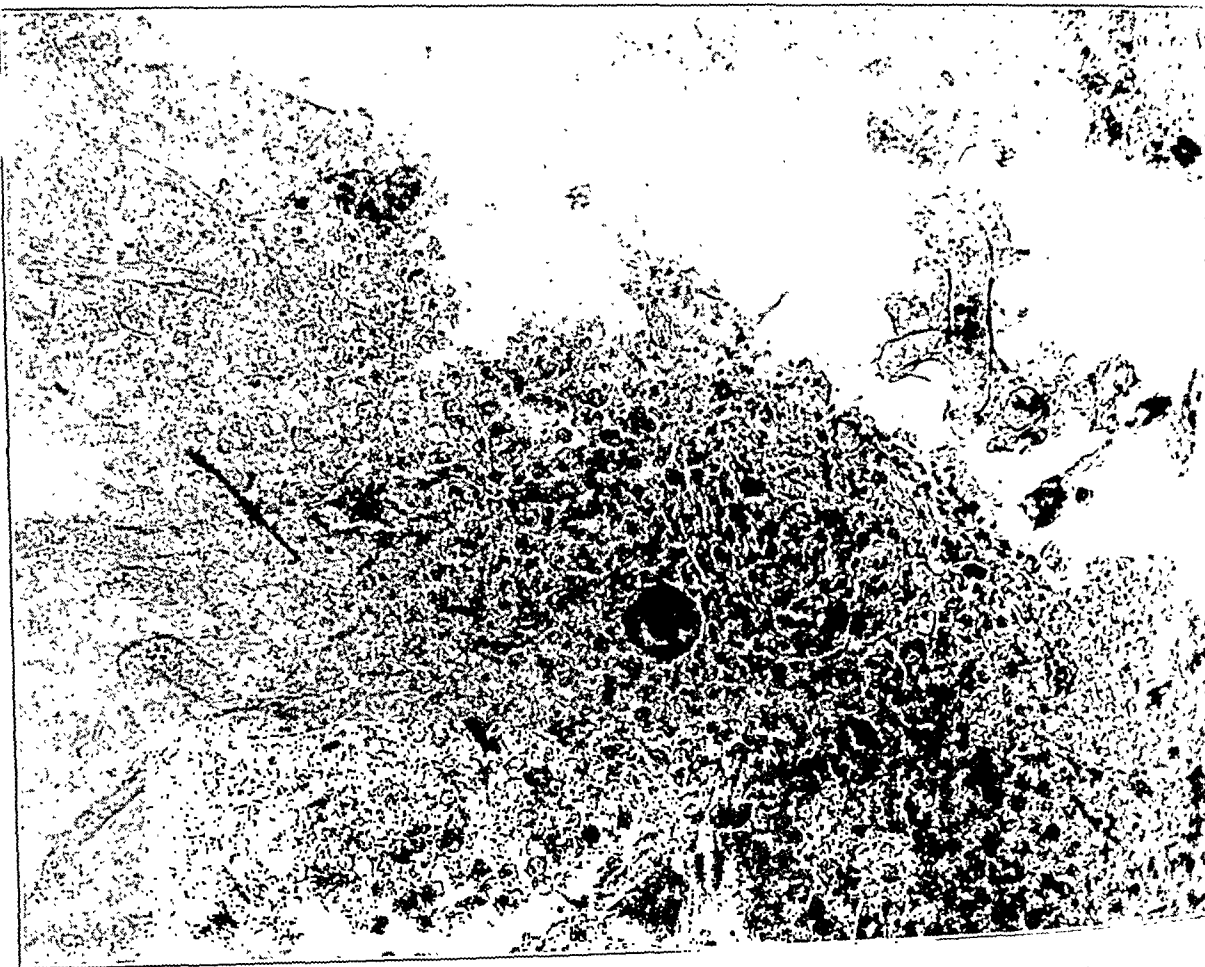


Fig. 4.—Photomicrograph of a section of the brain of a cat fourteen days after injury. Further astrocyte and microglial reaction is shown. The central collagen core can be seen.

and finally (3) brain deformity, often demonstrable by aerograms of the ventricular cavities.

Some of the stages of this process are depicted in the accompanying photographs.

Secondary to brain laceration, the ventricular system is pulled toward the side of the lesion (scar), and there is usually dilatation of the entire ventricular system (especially the first, second and third

ventricles) which is especially marked on the side of the lesion. This finding is interesting when compared with a series of ventricular "pictures" produced by extradural sterile foreign bodies (comprising approximately 4 per cent of the intracranial volume) pressing into the brain. In this series the ventricle on the side of the lesion is invariably found collapsed and pushed over toward the opposite side, while the contralateral ventricle is usually dilated.

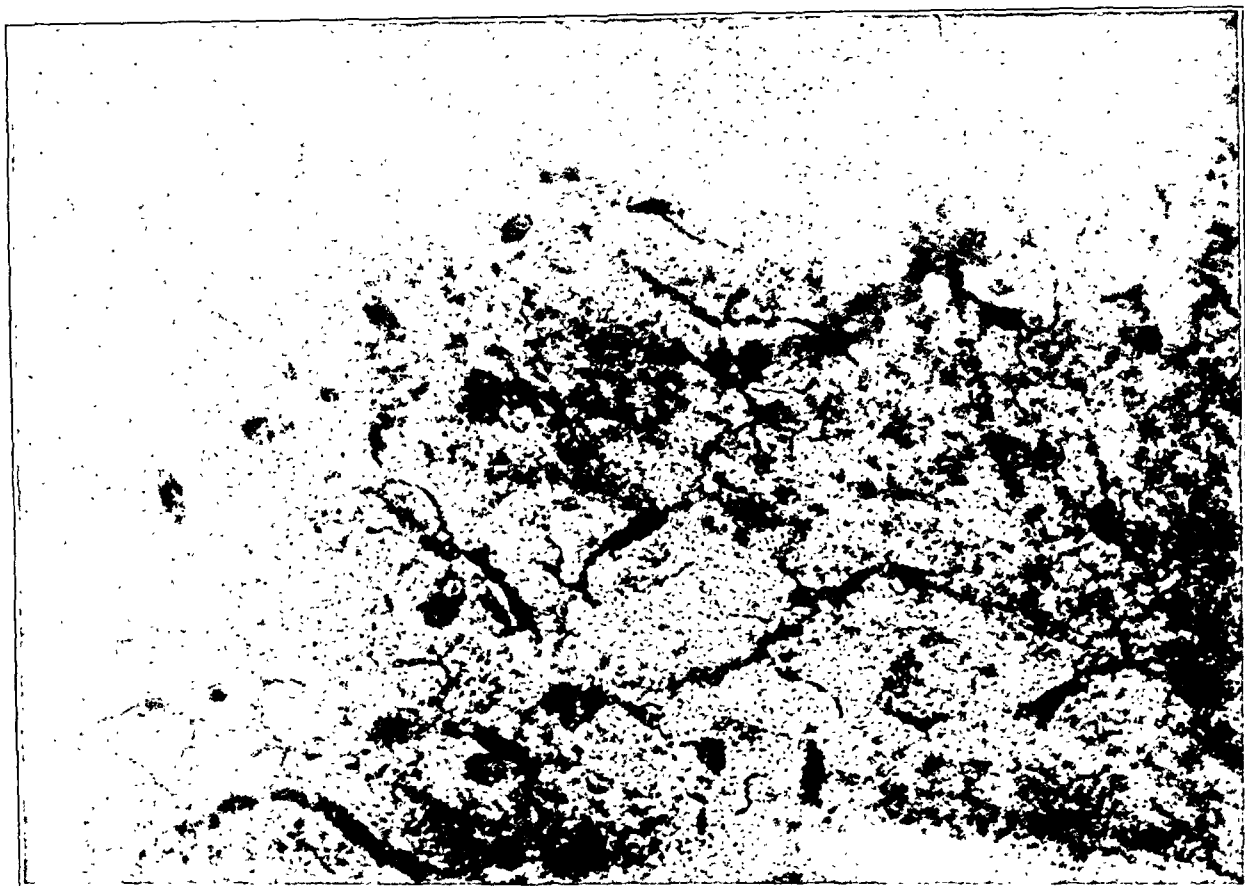


Fig. 5.—Photomicrograph of a section of the brain of a cat thirty-one days after injury. The brain cortex is shown in the region of the injury. Stained to show microglia.

All the animals that were subjected to the brain laceration previously described had deformity of the ventricles. Of twenty-four animals subjected to skull fracture, nine had misshapen ventricles (of which seven had visible meningocerebral adhesions). Of six animals in which blood was introduced into the subarachnoid spaces, all had normal ventricles. Bagley, working with very young puppies, was able to demonstrate ventricular distortion secondary to repeatedly introducing blood into the subarachnoid spaces. He also mentioned the infrequency

of ventricular distortion following subsection of adult dogs to the same procedure.

All these findings help in a better interpretation of the "post-traumatic state." A brain subjected to trauma, depending on the

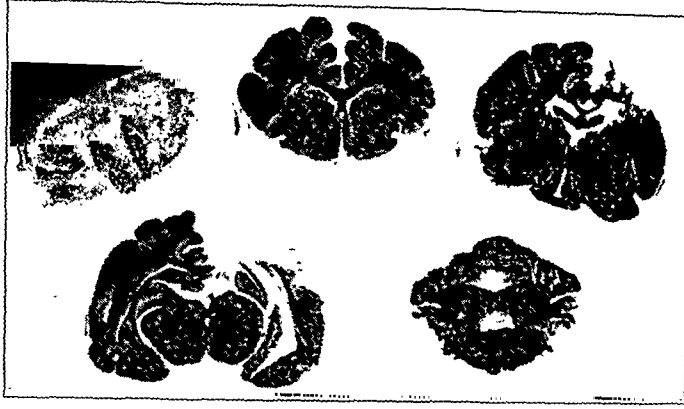


Fig. 6.—Specimen 46 VD obtained Jan. 13, 1931. The lesion was made on Oct. 10, 1930. There was a meningeocerebral scar over the left parieto-occipital cortex. The ventricle directly underneath is dilated and pulled up by the adherent scar.

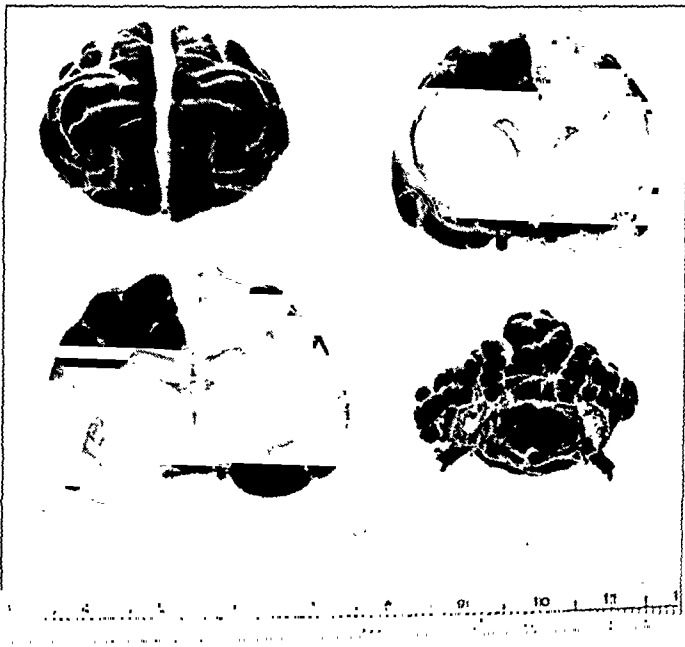


Fig. 7.—Specimen no. 85 from the series of animals with skull fracture. There is a moderate degree of internal hydrocephalus present. The specimen was obtained ninety-four days after injury.

severity of the injury, may become hypersensitive to stimulation that otherwise would not affect it. This condition may persist for varying time periods, dependent on underlying histopathologic changes. The more severe instances of brain trauma undoubtedly give rise to a greater

percentage of convulsive episodes, and probably depend on preexistent cerebral laceration producing meningocerebral adhesions.

#### SUMMARY AND CONCLUSIONS

Aseptic brain laceration, blood in the subarachnoid spaces and skull fracture (which may give rise to one or both of the aforementioned conditions) result in the following:

1. There may be an increased sensitiveness to a standardized convulsant camphor monobromide (in neurotoxic doses) which can be demonstrated four days after injury and which persists for approximately from three to four months. Some animals remain hypersensitive to camphor after this time; others return to a normal level.

2. There may be meningocerebral adhesions and contracting cerebral cicatrix.

3. The latter conditions (2) may produce distortions of the cerebral ventricular system.

# VERTEBRAL OSTEOCHONDRITIS

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Vertebral osteochondritis is a disease of the body of the vertebra which occurs during the first decade of life and is analogous to osteochondritis and epiphysitis occurring in other bones during the period of growth. The condition was described by Calvé<sup>1</sup> in 1924 and by Buchman<sup>2</sup> in 1927. In a more recent article, Calvé<sup>3</sup> reviewed the known instances, his summary disclosing the fact that only eight cases are on record. I shall present the history of a patient observed at the Willis C. Campbell Clinic in whom the clinical and roentgenologic manifestations correspond in every particular to those in the cases reported previously. This patient had, in addition to the spinal syndrome, a cyst in the upper end of the right femur.

## REPORT OF A CASE

*History.*—D. P., a boy, aged 4 years, was referred by his local physician for examination on Jan. 17, 1930. The chief complaints were a limp and pain in the right knee. The father and mother were healthy, and the family history was unimportant, except that an aunt had died of tuberculosis. Two months previous to the examination, the patient had had an attack of abdominal colic which persisted for about three weeks. One month later, the parents noticed that the child walked with a slight limp on the right side, and he complained of pain in the right knee. The pain became more severe and the limp more pronounced, so that for the three weeks before I saw him the child had not been allowed to walk. Rest partially relieved the symptoms. At times the temperature had been slightly elevated in the afternoon, and there had been progressive loss in weight since the onset.

*Examination.*—Examination showed a well developed, undernourished child. The right knee appeared normal. There was no redness, induration or swelling of the thigh, but there were moderate tenderness on deep palpation over the upper end of the right femur and limitation of motion in the hip due to muscular spasm.

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Read at the Annual Meeting of the Association of Resident and Ex-Resident Physicians of the Mayo Clinic, Rochester, Minn., Oct. 8, 1931.

1. Calvé, Jacques: A Localized Affection of the Spine Suggesting Osteochondritis of the Vertebral Body, with the Clinical Aspect of Pott's Disease, *J. Bone & Joint Surg.* 7:41, 1925.

2. Buchman, Joseph: Osteochondritis of the Vertebral Body, *J. Bone & Joint Surg.* 9:55, 1927.

3. Calvé, Jacques: Osteo-Chondrite Vertébrale Infantile, in the Robert Jones Birthday Volume: A Collection of Surgical Essays, New York, Oxford University Press, 1928, p. 315.

The legs were of equal length. When the child was walking, the right hip was held flexed and adducted, causing a limp. The gait was also guarded, resembling the characteristic attitude of tuberculosis of the spine, and voluntary movements of the spinal column were restricted. Passive motion of the spine was free, and there was no visible or palpable deformity. The results of physical examination were otherwise negative, except for moderate dental caries and hypertrophied tonsils.

A roentgenogram of the pelvis and both hips was made, and, in consideration of the possibility of Pott's disease with a psoas abscess, roentgenograms of the dorsal and lumbar spine were also requested. Two quite distinct and dissimilar lesions were found. In the upper end of the right femur there was a cyst extending into the neck of the femur (fig. 1). The cortex of the bone was not expanded,



Fig. 1.—Cavity in upper end of right femur resembling osteitis fibrosa cystica.

and there was no inflammatory reaction, as evidenced by production of new bone. The second lesion involved the body of the twelfth dorsal vertebra (fig. 2). The body of the vertebra was flattened, and the opacity of the bone was increased, resembling the appearance of the tarsal scaphoid bone in Köhler's disease. The height of the intervertebral disks above and below the lesion was increased. The remaining dorsal and lumbar vertebrae were normal.

The urine was clear and lemon-colored, with a specific gravity of 1.030; analysis was negative for albumin, sugar and casts; there were occasional epithelial and pus cells; red blood cells, crystals and bacteria were absent; there was a slight trace of acetone; the reaction to the test for mucus was 4+.

The differential blood count was: polymorphonuclear leukocytes, 53 per cent; lymphocytes, 43 per cent; eosinophils, 4 per cent, and hemoglobin, 69 per cent. The Wassermann reaction of the blood was negative. The inorganic calcium was 12 mg., and the inorganic phosphorus 3.6 mg., per hundred cubic centimeters of blood serum. The Pirquet reaction was negative.

The preoperative diagnosis was osteochondritis of the twelfth dorsal vertebra and osteitis fibrosa cystica of the right femur.

*Operation.*—An exploratory operation on the femur was performed five days after admission to the hospital. An incision was made over the greater trochanter, and a bone drill was passed into the cystic area in the femoral neck. The cyst contained a small amount of serous fluid, and on curettage flakes of a fibrous membrane and myxomatous tissue were removed. The cavity was thoroughly curetted and packed with chips of bone secured from the adjacent shaft of the femur. The wound was closed without drainage, and a plaster of paris cast applied, immobilizing the spine as well as the hip. Cultures of the serum and the membrane secured from the cavity were negative. The microscopic diagnosis was fibrous connective tissue, confirming the diagnosis of osteitis fibrosa cystica.

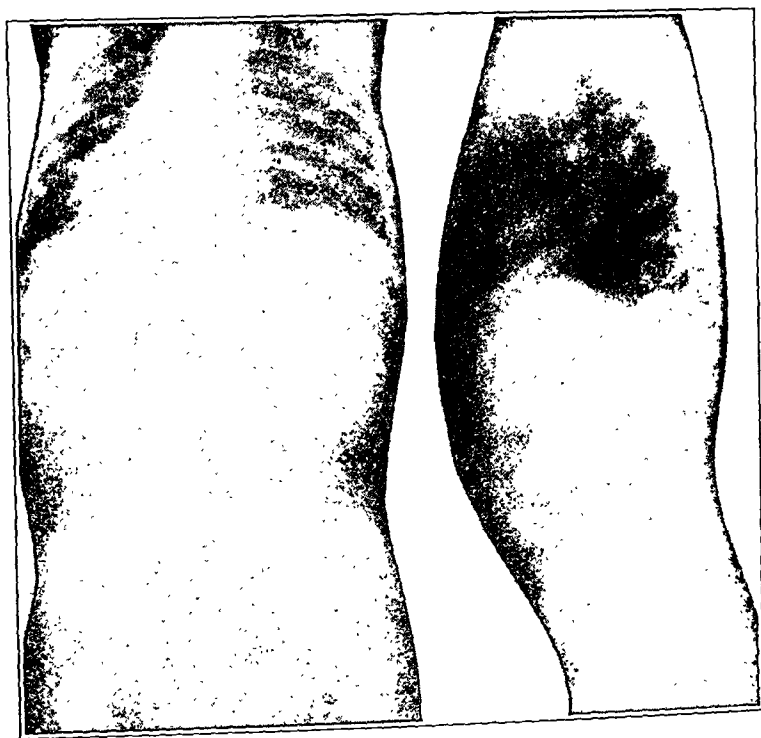


Fig. 2.—Flattening and condensation of the body of the twelfth dorsal vertebra; anteroposterior and lateral views. Note the preservation of the intervertebral spaces in the lateral view.

*Course.*—The child's temperature was elevated to about 100 F. for several days following the operation. It then subsided and remained normal throughout his stay in the hospital. Three weeks after the operation the cast was changed, and the wound was found to be healed by primary intention. The second cast was removed a month later, and a caliper brace applied to the leg and a leather corset with a head support to the spine. Heliotherapy was administered during the summer months, and a high vitamin diet, cod liver oil, viosterol and calcium lactate prescribed.

The child's general condition improved, he was able to walk about without discomfort wearing the brace, and on repeated examination motion of the spine and hip was found to be free and painless. Subsequent roentgenologic observation of the femur showed the cavity to be filled in with new bone and the normal osseous

structure to be restored gradually. In spite of the wearing of the brace, a mild rounded kyphos developed in the dorsal spine. On Jan. 12, 1931, almost one year after the first examination, roentgenograms of the spine revealed persistence of the flattening and increased density of the twelfth dorsal vertebra. There were observed at that time a similar flattening and opacity of the eighth dorsal vertebra, which had appeared normal in the original roentgenograms. Recumbency on a Bradford frame with the spine hyperextended was then advised. Roentgenograms of the spine made in May, 1931, revealed flattening of three dorsal vertebrae, i. e., the twelfth, the eighth and the third; the disease in the third vertebra developed during the interval that the spine was immobilized on the Bradford frame. The most recent observation was made on September 10. The child had then been on the frame for eight months. The spine was straight, painless and freely movable. Roentgenograms at that time demonstrated formation of new bone, with an



Fig. 3.—Eighteen months after figure 2, showing flattening of the third, eighth and twelfth dorsal vertebrae. Note the regeneration of the bone in the body of the twelfth dorsal vertebra in the lateral view.

attempt at regeneration of the twelfth dorsal vertebra. The contour of the bodies of the eighth and third vertebrae was similar to that found on the previous examination (fig. 3).

#### COMMENT

*Differential Diagnosis.*—The etiology of osteochondritis of the vertebral body is unknown. In the reported cases the age of incidence has varied from 20 months to 10 years. Males and females are affected in the same ratio. Tuberculosis can be excluded, because the disease involves the vertebral body, while the intervertebral disks remain intact. The greater opacity of the bone indicates that the density is increased.



The tuberculin test was negative in six of the nine cases in which mention of this test was made. Finally, successive roentgenograms, in the cases that have been followed through a period of several years, have shown constant regeneration by new bone until the vertebral body has reassumed almost its normal contour.

Syphilis can also be excluded, since the Wassermann reaction has been negative in four of the cases. In four cases the Wassermann reaction was not recorded, and in one case it was reported as doubtful.

The condition should not be confused with congenital malformation of the vertebral body. The malady is acquired after birth, being different in clinical and pathologic respects from congenital deformity. In addition, the case presented here is the third one on record in which early roentgenograms made before the deformity was present are available for comparison with those made after the flattening of the body had occurred.

Kummel's disease may be differentiated, because in none of the cases has there been a definite history of antecedent trauma.

The search for the etiology of the various forms of osteochondritis has led some authors to believe that rickets is a causative factor. Not only have clinical and roentgenologic studies failed to substantiate this assumption, but estimations have shown the blood calcium and phosphorus to be within normal limits.

*Etiology and Prognosis.*—The theory suggested by Calvé and by Buchman<sup>4</sup> seems to be the most acceptable and is analogous to that given for the deformity in the other epiphyseal diseases. This theory is that there is an imbalance between the static demand and the static capacity of the newly formed bone. Under the influence of some cause, which may be infectious or endocrine in origin, the body of a vertebra softens. The lessened resistance predisposes the bone to be crushed by the supercumbent weight of the body.

No attempt will be made to correlate the occurrence of the two pathologic conditions present in the case reported. Whether the lesions in the femur and vertebrae are distinct pathologic entities occurring simultaneously, whether the same unknown factor is the underlying cause of each, or whether they are identical lesions occurring in bones of different density and subjected to different functional strains and stresses, as has been suggested in the case of giant cell tumor and osteitis fibrosa cystica, remains undetermined. The known pathologic facts are limited to the roentgen findings. Biopsy of the vertebral body is not practical, and since the disease is not fatal, the opportunity for postmortem examination has not been available. In the roentgenogram

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4. Buchman, Joseph, and Gittleman, Isaac: *Inorganic Blood Chemistry in Osteochondritides*, Am. J. Dis. Child. **40**:1250 (Dec.) 1930.

in some cases the vertebral body may appear flattened, laminated and regular; in other cases it may be irregular and slightly wedge-shaped. The opacity is usually increased, indicating an increase in the density of the bone. The intervertebral spaces are intact and are actually wider than normal.

Vertebral osteochondritis is a true disease entity running a characteristic evolutionary course and tending toward spontaneous recovery with regeneration of the affected bone. The treatment consists of immobilization of the spine with appropriate apparatus, combined with general hygienic measures.

#### CONCLUSIONS

A case of vertebral osteochondritis is presented which is believed to be the ninth case on record.

Successive roentgenograms demonstrated the development of changes in two vertebrae that had been normal at the original examination. Regeneration of one vertebra is beginning one and one-half years after the onset. The other vertebra will probably show regeneration later.

The small number of cases reported suggests the probability that the condition is being mistaken for tuberculosis of the spine, an error similar to that made regarding coxa plana before that disease was differentiated from tuberculosis of the hip by Legg, Calvé and Perthes.

A favorable prognosis for complete recovery is warranted from the ultimate cure in similar conditions.

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# URETERODURAL ANASTOMOSIS FOR THE TREATMENT OF HYDROCEPHALUS

REPORT OF A CASE

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AND

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Our distressing helplessness in curing patients of hydrocephalus has led one of us (Dr. Davidoff) recently to review the treatments attempted for this condition from the days of Hippocrates to the present time.<sup>1</sup> Of all the remedies so far tried, it appeared to us that the operation reported by Heile<sup>2</sup> for cases of so-called communicating hydrocephalus is the most promising. This author has now reported a number of cases with very encouraging results. His operation, briefly, consists of unilateral nephrectomy followed by anastomosis of the upper end of the ureter (kidney pelvis) with an opening in the lumbar dura mater.

We have had occasion to test this method on one patient, and while the case was, on the whole, an unfavorable one, it served the purpose of demonstrating the mechanical feasibility of the ureterodural anastomosis.

## REPORT OF A CASE

*History.*—The patient, a child of 21 months, whose illness dated from birth, was the second born of middle-aged parents. The first child, born in 1926, died in one and one-half hours from "hydrocephalus." This second child was born with a mass at the nape of the neck, but appeared otherwise normal. At the age of 4 weeks (April, 1928) he was admitted to another hospital in this city because of the mass which had grown to the size of a grapefruit. The mass proved to be a

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From the Department of Surgery, Fifth Avenue Hospital.

1. Davidoff, Leo M.: Treatment of Hydrocephalus: Historical Review and Description of a New Method, *Arch. Surg.* **18**:1737, 1929.

2. Heile, B.: Zur Behandlung des Hydrocephalus, *Deutsche med. Wchnschr.* **24**:1468, 1908; Zur chirurgischen Behandlung der Spina bifida mit Hydrocephalus, *Berl. klin. Wchnschr.* **47**:2298, 1910; Zur chirurgischen Behandlung des Hydrocephalus internus durch Ableitung der Cerebrospinalflüssigkeit nach der Bauchhöhle und nach der Pleurakuppe, *Arch. f. klin. Chir.* **105**:501, 1914; Ueber neue operative Wege zur Druckentlastung bei angeborenen Hydrocephalus (Ureter-Duraanastomose), *Zentralbl. f. Chir.* **52**:2229, 1925; Zur Behandlung des Hydrocephalus mit Uretero-Duraanastomose, *Zentralbl. f. Chir.* **54**:1859, 1927.

meningocele which was removed two days after admission. The wound healed well but drained spinal fluid for two weeks. After operation, the circumference of the head was 40.5 cm. The size of the head increased steadily until it measured 48.2 cm. when the child was discharged from the hospital eight weeks later.

One cubic centimeter of indigo carmine injected into the right lateral ventricle just before discharge revealed no dye on lumbar puncture fifteen minutes later.

In spite of the advancing hydrocephalus, the child ate well and gained weight normally. On Aug. 7, 1928, at a neighboring institution, puncture of the corpus callosum was done, evidently with the hope of establishing a new pathway for the fluid to escape from the ventricles. This failed of the desired effect. On August 11, the head measured 51.5 cm. in circumference.

The child was then started on treatment with theobromin sodiosalicylate<sup>3</sup> for a period of about three months, at first actually reduced, and later at t checked the increasing size of the head.

Finally, in spite of the theobromin sodiosalicylate and bromides, the head eased in size, the child failed to develop mentally, began to have convulsive ures and gradually began to lose weight and strength.

*Admission.*—The patient was admitted to the Fifth Avenue Hospital on Jan. 7, 1930. By this time, his head had grown to a circumference of 60 cm. and seemed to gh more than all the rest of the child. He was undernourished, somewhat ydrated and rather irritable. The fontanels were widely open and bulging sely, and the sutures widely separated.

A dye test this time revealed incomplete but definite communication between the tricles of the brain and the spinal subarachnoid space. The condition was, of urse, desperate, and the prognosis so certainly fatal without some drastic thera- tic measure that it was decided to carry out the following operative procedure:

*Operation and Course.*—A left ureterodural anastomosis was performed on Janu- y 9. The operation was started with a left-sided nephrectomy (Dr. Bancroft), vascular pedicle of the kidney being tied and cut. Unfortunately, because of too ach tension on the kidney, the ureter tore off close to the pelvis. There appeared be sufficient length to continue the operation, however. The anterior part of e kidney incision was closed. The child was bent slightly toward a prone osition, and laminectomy was done (Dr. Davidoff), the dura being exposed er the length of three vertebrae. The ureter was now inserted between the uscle layers from the lateral incision to appear in the middorsal incision. Two lk sutures were taken in the ureter, one on either side, and this structure was hen split between the sutures. A probe was inserted in the lumen for orientation. small hole was now made in the dura, and the two split ends of the ureter were wwed by means of silk threads into this hole. A third suture was taken to anchor e ureter further into the dural defect. A considerable amount of cerebrospinal uid was lost during this stage of this procedure. This was accompanied by a epression in the fontanel. Closure was made of both wounds with interrupted o. 1 plain catgut sutures in several layers. The child's condition, while not very ood at the start, was not made any worse by the operation.

The child stood the operation rather better, on the whole, than might have een expected. The fontanels became concave, and the cranial bones began to verride. The general condition did not improve, however, and nine days after

3. Marriott, W. McKim: The Use of Theobromin Sodiosalicylate in the Treatment of Hydrocephalus, *Am. J. Dis. Child.* 28:479 (Oct.) 1924.



Fig. 1.—Film taken post mortem showing catheter in place in left ureter before injection of sodium iodide. The sharp outlines of the vertebrae are to be noted.



Fig. 2.—Film taken after injection of 20 cc. 15 per cent sodium iodide solution. The outline of the ureter (U) is seen as it curves around the lumbosacral muscles to join the dura. The outlines of the vertebrae are obliterated by the opaque medium filling the spinal canal.

operation, under local anesthesia, a rapid jejunostomy was done, with the hope of increasing the food and fluid intake. About twelve hours after this procedure, the child died.

Permission was granted for complete postmortem examination. Before proceeding to the general necropsy, a suprapubic cystostomy was done and a fine, soft catheter inserted into the left ureter. An x-ray picture showing the tube in situ was taken (fig. 1). Twenty cubic centimeters of 15 per cent sodium iodide was then injected into the catheter without meeting any notable resistance. A second x-ray picture showed the opaque medium filling the spinal canal to at least the cisterna magna (fig. 2), thus demonstrating the patency of the ureterodural anastomosis. The anastomotic area was then excised, and a histologic section made of the junction.

*Autopsy.*—Autopsy showed the head to be very much enlarged in its upper portion with wide separation of a very large anterior fontanel. On removing the skull cap, the brain was found enlarged and cystic and in places thinned out to a transparent shell; this was especially noticeable in the left parietal region. Section of the brain after hardening showed very much enlarged lateral ventricles, also enlargement of the third and fourth ventricles and aqueduct of Sylvius; just beneath the posterior commissure there was a centrally placed hard area 2 cm. in size with a yellowish necrotic-looking center. Microscopic examination of this hard area at the base of the brain revealed a fibrous capsule with a central necrotic looking portion showing cholesterol crystal spaces, suggesting an old hemorrhage. There were also areas of edema. The cerebellum was normal. Section through the thinned out cortex showed a narrow zone of gray matter. There was no evidence of acute inflammation or new growth.

The rest of the body showed nothing noteworthy, except for malnutrition and pulmonary edema.

#### COMMENT

A number of points of interest are presented by this case.

1. The dye test proves not to be absolutely reliable as a proof of permanent communication or obstruction between the ventricular system and the spinal subarachnoid space. In the patient whose case is reported the test showed complete block when done two years before, and nearly complete block during the time of his stay at this hospital; yet, when laminectomy was done, on incision of the lumbar sac a great excess of fluid escaped with resulting depression of the fontanels. It would seem to us that the most reliable method for testing the communication between ventricles and the spinal subarachnoid space would be a simple lumbar puncture. In the absence or scantiness of fluid, a block may be assumed, while a free flow of fluid, especially when accompanied by a sinking-in of the fontanels, must indicate a communication.

2. The justification of excising a healthy kidney may be found in the inevitably fatal outcome in a case of uninterrupted progressive hydrocephalus. Indeed, on the same grounds, the objection that urinary bladder infection might conceivably lead to meningitis at some future time must also be excused.

3. The stage of the disease at which success of the treatment might reasonably be looked for is, of course, a much earlier one than that at which the operation was done on this child. This we recognized, but hoped, nevertheless, that if we could not cure the child, we might, at least, test out the method.

4. Both by roentgenograms taken with an opaque medium and by gross and histologic examination, it was possible to show that a persistent communication can be established between the spinal fluid spaces of the lumbar region and a ureter, which may serve to drain the spinal fluid into the urinary bladder.

# SURGICAL TREATMENT OF MITRAL STENOSIS

## AN EXPERIMENTAL STUDY

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The technical difficulties and hazards of an operative procedure on the heart are great. Medical therapy in chronic cardiac valvular disease offers nothing but supportive and palliative treatment without hope of permanent relief. Consequently the surgical treatment of mitral stenosis presents a most fascinating and interesting problem to both surgeon and physician.

The rationale for the procedure has been based on the assumption that mitral insufficiency is functionally a less damaging lesion than mitral stenosis. With this hypothesis as a major premise, the first operation of election on the mitral valve was performed by Dr. Elliott C. Cutler<sup>1</sup> in May, 1923. A tenotome was inserted into the mitral orifice through the left ventricle, and an attempt was made to incise each segment of the obstructing ring. The patient recovered and was definitely improved until the onset of a terminal illness four and one-half years later.

After this first intrepid effort, Allen and Graham<sup>2</sup> attempted a three-stage procedure with an instrument carrying an optical system, by which they hoped to cut the valve under direct vision. The patient died on the operating table.

The experience gained in their first and two subsequent cases convinced Cutler and Beck<sup>3</sup> of the impossibility of enlarging the mitral orifice sufficiently with a simple knife to obtain an adequate degree of regurgitation. Consequently the cardiovalvulotome<sup>4</sup> was developed, a

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This study was aided by a grant from the DeLamar Mobile Research Fund. From the Laboratory for Surgical Research, Harvard Medical School, Boston.

1. Cutler, E. C., and Levine, S. A.: *Cardiotomy and Valvulotomy for Mitral Stenosis*, Boston M. & S. J. **188**:1023, 1923.

2. Allen, D. S., and Graham, E. A.: *Intracardiac Surgery—A New Method*, J. A. M. A. **79**:1028 (Sept. 23) 1922.

3. Cutler, E. C.; Levine, S. A., and Beck, C. S.: *The Surgical Treatment of Mitral Stenosis, Experimental and Clinical Studies*, Arch. Surg. **9**:689 (Nov.) 1924.

4. Beck, C. S., and Cutler, E. C.: *A Cardiovalvulotome*, J. Exper. Med. **40**: 375 (Sept.) 1924.



powerful cutting instrument by which a segment of the valve could be excised and removed from the circulation.

With one exception all subsequent operations have been performed with this instrument. The exceptional, and only successful, case is that reported by Souttar,<sup>5</sup> in which the mitral orifice was dilated with the finger, introduced through the left auricular appendix. This patient is living and apparently improved.

In all, ten patients with mitral stenosis have been subjected to surgical treatment. The mortality has been 90 per cent. Except in Cutler's first case, death occurred from three hours to six days after operation, and in the majority of instances was due, not to operative shock, but to cardiac failure. The mechanical difficulties of the operation have been overcome, mitral insufficiency has been created both by incising the stenotic orifice and by excising a segment of the sclerosed valve, and yet the patients have died. The question presents itself, therefore: Is valvulotomy or partial valvectomy a feasible and justifiable operation in patients with mitral stenosis?

It is undeniably true that an insufficient valve is a more tolerable valve from the patient's standpoint than a stenotic one. Furthermore, Cutler and his collaborators showed experimentally that mitral regurgitation was well tolerated by normal dogs. One may reasonably assume, however, that the physiologic alterations that take place in the circulation after the excision of a segment of normal valve do not approximate those which obtain when a defect of similar degree is made in the thickened and sclerotic post-rheumatic valve. The facts suggest that an embarrassed cardiac mechanism, laboring under the mechanical difficulties of a chronic mitral obstruction, is unable to tolerate the additional insult of a sudden, superimposed regurgitation, and death occurs from cardiac failure.

The experiments presented here are offered in support of this contention.

#### EXPERIMENTAL METHODS

Since the development of a method for creating chronic cardiac valvular disease in dogs,<sup>6</sup> certain phases of the problem, which previously were restricted to clinical impressions and observations on patients, have become amenable to precise physiologic study in the laboratory. Four distinct procedures have been carried out:

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5. Souttar, H. S.: The Surgical Treatment of Mitral Stenosis, *Brit. M. J.* 2: 603, 1925.

6. Powers, J. H.: The Experimental Production of Mitral Stenosis, *Arch. Surg.* 18:1945 (April) 1929.

1. Experimental stenosis of the mitral valve has been produced in dogs, a chronic, sclerosing lesion which, in its mechanical and gross pathologic aspects,<sup>7</sup> is comparable with mitral stenosis in man.

2. Physiologic observations have been made on the circulation of these animals with experimental mitral stenosis.

3. The stenosis has been abruptly converted into insufficiency by partial valvulotomy with the cardiovalvulotome.

4. The physiologic observations have been repeated to determine what effect this procedure has on the mechanics of the circulation, and why the sudden transformation of chronic mitral stenosis into stenosis with insufficiency should be incompatible with life.

1. *Production of Mitral Stenosis.*—The method has been described in detail elsewhere.<sup>6</sup> In brief, two distinct maneuvers were carried out: (a) electrocoagulation of the mitral valve and (b) subsequent intravenous inoculation with cultures of *Streptococcus viridans*.

(a) The dog was anesthetized with ether administered intratracheally by the mechanical respiratory apparatus. The heart was exposed by subperiosteal resection of a portion of the left fifth rib. The active electrode of a high frequency unit delivering a bipolar current was introduced into the left ventricle and the tip approximated to the mitral ring and inferior surface of the segments of the valve. The current was applied for one to three seconds. The electrode was then withdrawn and the wound was closed in layers with silk.

(b) During the early postoperative course the animal was inoculated intravenously with fresh broth cultures of *Streptococcus viridans*.<sup>8</sup> The development of accentuated cardiac sounds, a systolic murmur and positive blood cultures for several months were considered indicative of an acute vegetative endocarditis of the mitral valve. As the lesions healed, the organisms disappeared from the blood stream. The animal was then operated on again in the same manner and reinoculated with larger doses of *Streptococcus viridans* than before. Negative blood cultures were obtained relatively soon after the second operation, presumably because of resistance developed in overcoming the original infection.

When this stage of the problem had been completed, five male dogs with experimental mitral stenosis were alive and in good health. At the second operation, multiple scars and some stenosis of the orifice were palpable in each case. Consequently there could be no question about the presence of a chronic sclerosing lesion of the valve, in spite of the fact that this was not always borne out by the clinical evidence of a diastolic murmur.

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7. Powers, J. H.: Experimental Cardiac Valvular Disease in Dogs, and Subacute and Chronic Cardiac Valvular Disease in Man, *Arch. Surg.* **21**:1 (July) 1930.

8. Dr. Hans Zinsser furnished the strain of organisms, which was isolated from the myocardium of a child who died of rheumatic fever.

2. *Physiologic Observations.*<sup>9</sup>—Each animal was trained to lie quietly during all experimental procedures. All observations were made in the supine position. The legs were gently immobilized in extension by web straps attached to the sides of the table. Determinations were not carried out until the animal had been on the table approximately one-half hour.

With the animal under basal metabolic conditions, observations were made on the pulse rate, the blood pressure and the consumption of oxygen.

Immediately thereafter, samples of arterial and venous blood were drawn as nearly simultaneously as practicable from the left and right ventricles or from the femoral artery and right ventricle respectively. The blood was deposited under oil, mixed with an anticoagulant and analyzed in duplicate in the Van Slyke-Neil constant volume, manometric apparatus for the content of oxygen.

The cardiac output was determined according to the principle of Fick, which states that the volume of blood passing through the lungs in cubic centimeters per minute equals:

$$\frac{\text{cc. of oxygen consumed per minute}}{\text{amount of oxygen absorbed by 1 cc. of blood}}$$

The stroke output, or systolic discharge, was found by dividing the cardiac output per minute by the pulse rate.

X-ray films of the heart were exposed from a distance of 1 meter. The animal was allowed to lie quietly on its abdomen with the legs in extension. The plate was in contact with the anterior thoracic wall and the tube was centered over the midportion of the dorsal spine.

All these studies, except the last one, were repeated one or more times at varying intervals. Satisfactory determinations, checked within the limits of experimental error, thus were obtained.

3. *Partial Resection of Stenosed Mitral Valve.*—Each animal was then operated on a third time. The heart was reexposed through the healed scars of both previous incisions in the left thoracic wall. Adhesions between the pleura and lungs or lungs and pericardium were divided by sharp dissection whenever necessary. The pericardium was incised and freed from the anterior wall of the left ventricle. Control sutures were placed, the myocardium was incised and the cardiovalvulotome<sup>10</sup> was introduced into the left ventricle. By palpation of the mitral orifice through the roof of the left auricle, a scarred segment of the obstructing valve was engaged between the jaws of the instrument, excised and withdrawn from the circulation. Occasionally two or three bites of tissue were removed. The wound was then closed in layers with silk.

4. *Repetition of Physiologic Studies.*—All the physiologic studies described were then repeated. Dogs X3 and X5 died so unexpectedly during the immediate post-operative convalescence that no observations were obtained on these two animals. In order not to lose the opportunity for making determinations in the three remaining animals during this critical period, observations were begun directly after their recovery from anesthesia and were continued until death occurred.

9. This phase of the work has been reported recently (Powers, J. H.; Pilcher, C., and Bowie, M. A.: Some Observations on the Circulation in Experimental Mitral Stenosis, *Am. J. Physiol.*, to be published).

10. The instrument, a gift to the author by Dr. E. C. Cutler, carried a shaft of smaller diameter than the one used on patients, but was otherwise similar to it in all respects.

One control experiment was performed for the purpose of studying the effect on the circulation of partial resection of a normal valve. A normal male dog (X25) was trained to lie quietly on the table while the physiologic studies already outlined were carried out. The animal was then operated on and a portion of the mitral valve was excised with the cardiovalvulotome. The dog made a good convalescence. The preoperative studies were repeated at intervals during this period until the animal was killed, on the twelfth day.

#### EXPERIMENTAL DATA

EXPERIMENT 1.—In dog X3, a male, mongrel Irish terrier, weighing 14.1 Kg., electrocoagulation of the mitral valve was performed on March 19, 1928. The animal was inoculated intravenously several times with cultures of *Streptococcus viridans*. Positive blood cultures were obtained during the next four months. Examination of the heart revealed a rapid rate and forceful impulse. The first

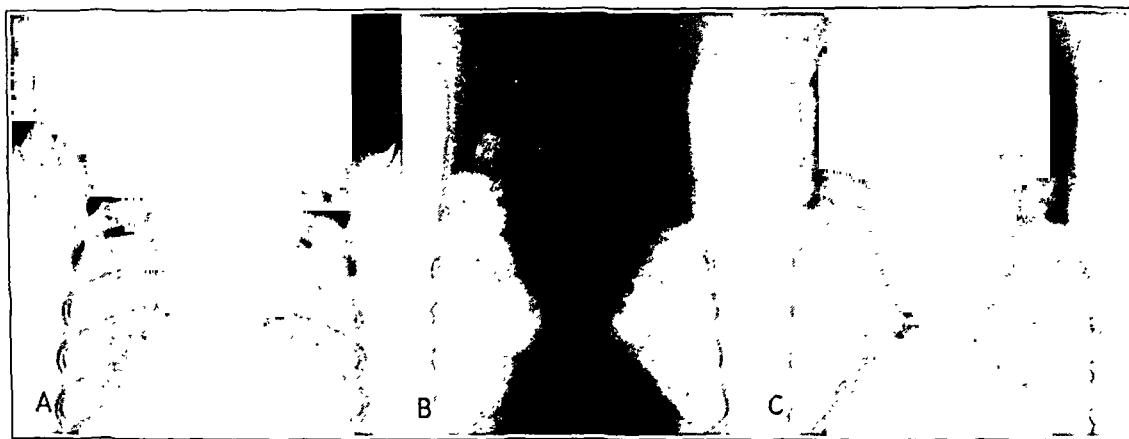


Fig. 1.—Roentgenograms of the heart of dog X3, taken on March 11, 1928 (A), September 7 (B) and Feb. 21, 1929 (C). The first plate was taken prior to operation and shows the normal cardiac size. Note the enlargement, particularly of the right side, that occurred with the development of mitral stenosis.

sound was snapping and valvular in quality. There was a soft systolic murmur. No diastolic murmur was audible.

At the second operation, on September 26, two scars were palpable in the posterior aspect of the mitral ring. The orifice was partially obstructed. The valve was cauterized again, and the wound was closed in layers with silk. After reinoculation, the blood culture was negative on the seventeenth postoperative day.

Four months later, three detailed series of physiologic observations were made according to the methods already outlined. The basal pulse rate was elevated to 120 beats per minute. All the other determinations were within the limits of normal.<sup>9</sup> The transverse cardiac diameter had increased 1.1 cm. (fig. 1). Auscultation disclosed systolic and early diastolic murmurs. The first sound was loud and snapping in quality.

Partial resection of the mitral valve was performed on May 2, 1929. Several dense scars were palpable in the mitral orifice. One of these was engaged between the jaws of the instrument, excised and withdrawn from the circulation (fig. 2). There was an immediate moderate dilatation of the heart and a marked increase in

rate. It was impossible to close the pericardium without embarrassing the cardiac impulse. The pleura and thoracic wall were sutured in layers with silk. At the end of the operation the dog's circulation was at a low ebb, its pulse rate approximately 200. A loud, blowing systolic murmur was audible. In the afternoon the animal recovered from the anesthesia, but was unable to stand. The respirations were rapid and shallow. At 8 a. m. the following day the dog was standing up in his cage and appeared to be in fairly good condition although the respiratory rate and pulse rate were still very rapid. One hour later he was found dead.

*Autopsy.*—There was a moderate amount of frothy blood in the respiratory passages; acute pulmonary congestion and edema were present. Each pleural cavity contained about 50 cc. of serosanguineous fluid. The heart was intensely engorged and dilated, particularly on the right side. There were no emboli in the pulmonary vessels. The liver was acutely congested.

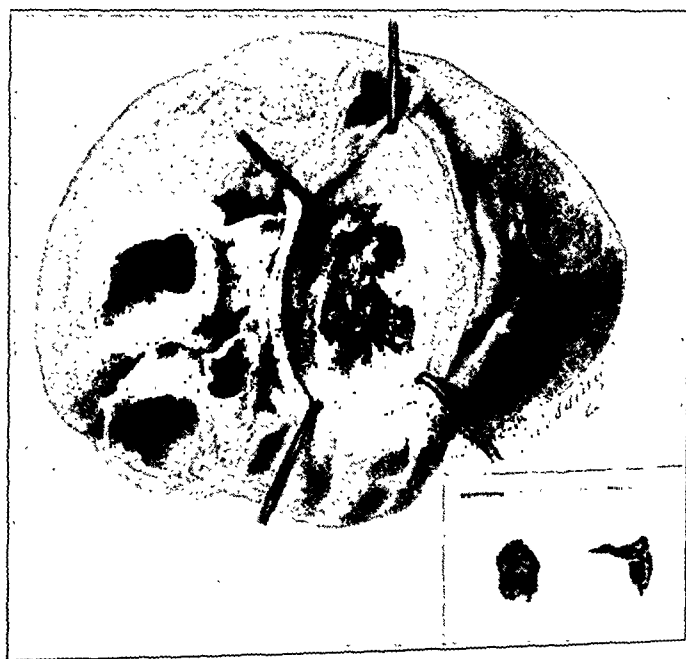


Fig. 2.—Heart of dog X3. The roof of the left auricle has been removed to expose the mitral valve. There is a large defect in the lateral leaflet. The insert shows the auricular and sagittal views of the segment that was excised with the cardiovalvulotome.

After removal of the heart, the roof of the left auricle was excised to expose the mitral valve (fig. 2). There were moderate constriction of the orifice and marked thickening of the lateral segment of the valve. A large defect was present in this segment.

*Comment.*—No postoperative physiologic studies were obtained. Death occurred seventeen hours after operation and was attributed to acute cardiac failure.

EXPERIMENT 2.—In dog X5, a male, mongrel Spitz, weighing 9.2 Kg., electrocoagulation of the mitral valve was performed on June 6, 1928. Acute endocarditis followed two intravenous inoculations with cultures of *Streptococcus viridans*. Organisms were recovered from the blood stream at intervals during the next two

months. Examination of the heart disclosed a snapping first sound and systolic and early diastolic murmurs.

The second operation was performed on September 10. Palpation of the mitral valve through the roof of the left auricle revealed several dense scars and some narrowing of the orifice. The valve was again traumatized with the electrocautery. The animal was given two postoperative inoculations with *Streptococcus viridans*, and the blood culture was positive during the following month.

Physiologic observations made six months later were all within the limits of normal. The transverse cardiac diameter had increased from 6.3 to 8.0 cm. (fig. 3). A soft systolic murmur was audible; a diastolic thrill was palpable.

Partial resection of the mitral valve was performed on May 15, 1929. The lateral leaflet of the valve was definitely thickened and sclerosed and the orifice was moderately obstructed. Three small segments of this portion of the valve were excised with the cardiovalvulotome (fig. 4). This was followed by an immediate

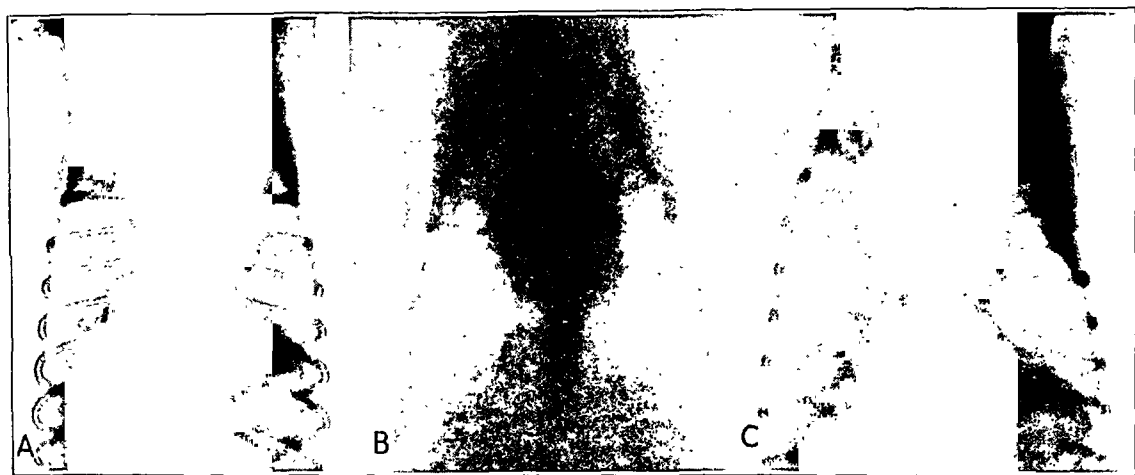


Fig. 3.—Roentgenograms of the heart of dog X5, taken on June 6, 1928 (A), September 7 (B) and April 8, 1929 (C). A marked increase in cardiac size is apparent in the last plate, taken five weeks before partial valvulectomy was performed.

dilatation of the whole heart and a marked increase in rate. No attempt was made to close the pericardium; at the end of the operation a loud systolic murmur was audible. The pulse rate was approximately 170. The dog recovered consciousness in the early evening, but was unable to stand. The respirations were shallow and rapid and the circulation was extremely poor. Death occurred during the night.

*Autopsy.*—Marked dilatation and engorgement of the heart, especially on the right side, and acute congestion and edema of the lungs were present. There was a small amount of serosanguineous fluid in each pleural cavity. The liver and spleen showed acute and chronic passive congestion. Examination of the mitral orifice from above revealed a large defect in the lateral segment of the valve (fig. 4).

*Comment.*—Unfortunately, death occurred so soon that no post-operative physiologic observations were obtained in this case either.

With each of these animals the postoperative course was similar to that observed in patients after partial valvectomy. The diagnosis of death from cardiac failure is supported both by the clinical observations during the immediate postoperative period and by the changes found at necropsy.

EXPERIMENT 3.—In dog X11, a male, mongrel bull terrier, weighing 12.5 Kg., electrocoagulation of the mitral valve was performed on May 3, 1928. The dog received two inoculations with cultures of *Streptococcus viridans* on the second and fourth postoperative days. Negative blood cultures were obtained two and one-half months later. Examination of the heart showed a rapid rate, a snapping first sound and both systolic and diastolic murmurs.

The second operation was performed on September 27. Two small dense scars were palpable on the anterior aspect of the mitral valve. Further traumatiza-



Fig. 4.—Heart of dog X5, with the roof of the left auricle removed to expose the mitral valve from above. A marked regurgitation is apparent. The insert shows the three small segments that were excised.

tion was carried out with the electrocautery without difficulty. After two large inoculations with cultures of *Streptococcus viridans*, the blood culture was negative in two weeks.

Physiologic observations on the circulation were made in June and August of the following year (table 1). The cardiac output was increased above the normal for an animal of this size.<sup>9</sup> The transverse cardiac diameter had increased 1.9 cm.

Partial resection of the mitral valve was performed on Dec. 12, 1930. Direct examination of the mitral orifice through the wall of the left auricle disclosed three palpable scars. Three attempts to remove a portion of the valve were made with the cardiovalvulotome, and at the third effort a section of thickened and fibrous valve was excised. The heart suddenly dilated so that closure of the pericardium was not possible. At the end of the operation the circulation was extremely sluggish and the heart rate was very rapid; a loud systolic murmur was audible.

In order not to lose the opportunity for making observations on the circulation of this animal during the immediate postoperative course, these studies were carried out one hour after the operation had been completed.

Death occurred suddenly, two hours later.

*Autopsy.*—About 50 cc. of liquid blood was found in each pleural cavity; the myocardial wound was firm; the heart was dilated and the right side tensely engorged with blood. The liver showed evidence of chronic passive congestion. Two old infarcts were found in the left kidney. Examination of the mitral valve from above showed a defect in the lateral segment, several fibrous scars and some thickening of the medial segment, but less actual stenosis of the orifice than was found in the two previous cases. Death was attributed to acute cardiac failure.

*Comment.*—These postoperative studies (table 1) afford some interesting data on the alterations in the circulatory mechanics induced by

TABLE 1.—*Physiologic Observations on the Circulation of Dog X11 (a Mongrel Bull Terrier Weighing 12.5 Kg.) Before and After Partial Valvulectomy for Mitral Stenosis\**

Date	Pulse Rate per Min.	Blood Pressure, Mm. Hg	Oxygen Consumption, Cc. per Min.	Arterial Oxygen	Venous Oxygen	Oxygen Utilization, per Cent by Vol.	Cardiac Output, Cc. per Min.	Stroke Output, Cc. per Beat	Comment
6/ 6/29	110	200/ 80	162.5	23.50	19.40	4.10	3,965	36.2	
8/14/29	126	180/ 80	141.9	27.35	23.00	3.45	4,110	32.6	Snapping first sound
8/26/29	128	190/ 90	171.5	27.19	22.89	4.30	4,055	31.6	Long low-pitched systolic murmur; systolic thrill
12/ 9/30	112	160/110	160.31	22.74	18.20	4.54	3,530	31.5	
12/12/30 10:30 a.m.		Operation: Partial resection of mitral valve							Three scars palpable in mitral orifice
12/12/30 1:00 p.m.	200	100/ 50	111.96	16.85	6.41	10.44	1,070	5.25	Animal unable to stand; rapid, shallow respirations
12/12/30 3:15 p.m.	Death. Autopsy: pulmonary congestion; congestion of liver; engorgement and dilation of heart; infarcts of kidney								

\* Profound changes are apparent after the production of mitral insufficiency. Death from cardiac failure was imminent when these studies were made.

suddenly releasing a chronic obstruction at the mitral orifice. A marked decrease was found in the consumption of oxygen, in the content of oxygen in arterial and venous blood, in the cardiac output per minute and in the stroke output. Both the pulse rate and the utilization of oxygen were greatly increased.

EXPERIMENT 4.—In dog X12, a male, mongrel bull terrier, weighing 17 Kg., electrocoagulation of the mitral valve was performed on May 4, 1928. No murmur was heard immediately after operation. Following two inoculations with cultures of *Streptococcus viridans* a loud systolic murmur was audible, which was undoubtedly due to the formation of septic thrombi on the traumatized valve. Positive blood cultures were obtained at intervals during the next four months.

The dog was then operated on again and reinoculated during the early postoperative course. Organisms disappeared from the blood stream in one month. Examination of the heart showed a systolic murmur and thrill. No diastolic murmur was audible. Six months later a detailed series of physiologic observations was carried out (table 2). All determinations were within the limits of normal.



Partial resection of the mitral valve was performed on May 2, 1929. One dense, thickened portion of the valve was removed. About 250 cc. of blood was lost. The pericardium was only partially closed. A rough, blowing systolic murmur was audible at the end of the operation. Physiologic studies were begun immediately, and are presented in detail in table 2. Evidence of a failing circulation was appar-

TABLE 2.—*Physiologic Observations on Dog X12 (a Mongrel Bull Terrier, Weighing 17 Kg.) \**

Date	Pulse Rate per Min.	Blood Pressure, Mm. Hg	Oxygen Consumption, Cc. per Min.	Arterial Oxygen	Venous Oxygen	Oxygen Utilization, per Cent by Vol.	Cardiac Output, Cc. per Min.	Stroke Output, Cc. per Beat	Comment
4/13/29	70	170/115	119.8	22.81	17.69	5.12	2,340	33.4	Cardiac sounds snapping in quality; high-pitched
4/16/29	72	150/ 90	127.3	21.59	16.71	4.88	2,610	36.2	Systolic murmur audible; systolic thrill
4/18/29	78	170/100	130.4	23.12	18.28	4.84	2,695	34.5	
4/25/29	72	.....	125.6	21.66	16.63	5.03	2,500	34.7	
5/ 2/29 2:00 p.m.			Operation: Partial resection of mitral valve						
5/ 2/29 5:00 p.m.	160	0	168.7	19.08	12.69	6.39	2,640	16.5	Blood volume determined just before operation; about 250 cc. of blood was lost; cardiac sounds weak; circulation poor
5/ 2/29 8:00 p.m.	210	0	173.7	17.64	10.86	6.78	2,560	12.2	
5/ 2/29 11:30 p.m.	230	0	147.2	16.21	10.01	6.20	2,375	10.3	Bled 200 cc., with some improvement
5/ 3/29 9:00 a.m.	180	95/ 75	154.4	15.44	6.31	9.13	1,690	9.4	Dog unable to stand; respiration rapid; no edema
5/ 3/29 11:00 p.m.	180	.....	126.0	14.30	6.43	7.87	1,600	8.8	Condition about same; dog unable to eat or drink
5/ 4/29	180	.....	137.8	10.90	4.30	6.60	2,085	11.6	Animal somewhat improved; brighter and stronger
5/ 5/29	140	100/ 30	128.3	11.24	4.42	6.82	1,850	13.4	Able to stand and drink water; circulation improved
5/ 6/29	160	.....	136.8	12.44	6.61	5.83	2,345	14.6	
5/ 7/29	160	.....	151.8	11.90	6.76	5.14	2,955	18.4	Bronchial breathing; coarse râles at base of right lung
5/ 9/29	136	120/ 70	138.2	12.24	5.65	6.59	2,095	15.4	Râles more numerous; no apparent peripheral edema
5/11/29	Death. Autopsy: marked dilatation of heart; pulmonary edema; pleural effusion; congestion of liver; ascites								Dog found dead in cage

\* The long series of postoperative determinations represents gradual changes in the circulatory mechanics occurring with partial decompensation. The steady decrease in arterial and venous oxygen and the gradual reduction in cardiac output per minute and per beat during the first two postoperative days is striking. As partial compensation was gained, the total cardiac output returned to normal, only to fall again with the occurrence of secondary failure.

ent in the rapid respiratory rate and a gradually decreasing cardiac output per minute and per beat. In the hope of relieving the burden on the heart, 200 cc. of blood was withdrawn. The dog was unable to stand. The second postoperative day his condition was somewhat improved clinically, and a corresponding increase was noted in the cardiac output per minute and per beat. A slow but gradual improvement occurred up to the fifth postoperative day, at which time the cardiac output was elevated above the preoperative level. Pulmonary congestion developed,

however, and both clinical and physiologic evidence of a failing circulation were again apparent. Death occurred on the ninth postoperative day.

*Autopsy.*—Frothy, blood-streaked mucus was noted in the nostrils. The wound was firmly healed. The right pleural cavity contained 40 cc. and the left pleural cavity 60 cc. of serosanguineous fluid. The lower lobes of both lungs were almost solid and "waterlogged." On section, great quantities of fluid escaped. There was no gross evidence of pneumonia. No pulmonary emboli were found.

The heart was enormously dilated, likewise both cavae. Examination of the mitral valve from above showed a large defect in the lateral segment. The orifice was moderately contracted, and the leaflets of the valve were definitely thickened and sclerosed.

The liver showed evidence of chronic passive congestion. The cortex of both kidneys was studded with small infarcts of various ages. Death was attributed to acute cardiac failure.

TABLE 3.—*Observations on Dog X15 (a Mongrel Bull Terrier, Weighing 17 Kg.) \**

Date	Pulse Rate per Min.	Blood Pressure, Mm. Hg	Oxygen Consumption, Cc. per Min.	Arterial Oxygen	Venous Oxygen	Oxygen Utilization, per Cent. by Vol.	Cardiac Output, Cc. per Min.	Stroke Output, Cc. per Beat	Comment
6/ 3/29	76	.....	136.3	22.23	14.10	8.13	1,675	22.0	
6/ 6/29	68	210/110	117.9	18.99	13.09	5.90	1,995	29.3	
6/11/29	72	190/ 95	104.4	18.66	12.38	6.28	1,665	23.1	
12/ 5/30	72	160/ 90	136.34	23.11	16.72	6.39	2,130	29.6	
12/ 8/30	72	150/100	114.51	21.39	16.36	5.03	2,275	31.6	No murmurs audible
12/10/30 10:30 a.m.		Operation: Partial resection of mitral valve							Orifice would not admit tip of index finger
12/10/30 2:15 p.m.	186	70/ 40	152.25	16.58	4.72	11.86	1,285	6.9	Circulation poor; respirations rapid and shallow
12/10/30 3:45 p.m.	Death. Autopsy: marked congestion of right auricle and ventricle; early pulmonary edema								Animal died slowly with labored and gasping respirations

\* The results are similar to those recorded in table 1.

*Comment.*—This animal lived nine days after partial valvulectomy. Consequently a long series of postoperative observations was obtained (table 2). These studies illustrate changes in the circulation occurring with a less acute cardiac failure followed by gradual, partial compensation, and succeeded finally by secondary failure and death. Decomensation developed more slowly during the immediate postoperative period than in either the foregoing or following experiments, and consequently the alterations in the circulatory mechanics were more gradual. Though less abrupt and perhaps less dramatic, the results, however, are equally convincing. It is unfortunate that a final series of determinations was not obtained just before death.

EXPERIMENT 5.—In dog X15, a male, mongrel bull terrier, weighing 17 Kg., electrocoagulation of the mitral valve was performed on May 29, 1928. After several intravenous inoculations with cultures of *Streptococcus viridans*, organisms

were recovered from the blood stream during the next three months. Examination of the heart during this period revealed no murmurs or thrills.

The second operation was performed on September 14. The dog was reinoculated twice in the usual manner. A negative blood culture was obtained one month later. Physiologic observations made in June, 1929, and December, 1930, checked within the limits of normal (table 3). During this period auscultation of the heart revealed no adventitious sounds, although direct palpation of the orifice at the second operation disclosed definite thickening and scarring of the mitral segments. The heart had increased 1 cm. in greatest transverse diameter.

Partial valvulotomy was performed on Dec. 10, 1930. The mitral orifice was definitely contracted and would not admit the tip of the index finger. A segment was removed from the lateral margin of the valve (fig. 5). The wound was closed as usual. A systolic thrill and loud systolic murmur were apparent immediately after the operation. Both the cardiac and respiratory rates were extremely rapid. One series of postoperative determinations was obtained (table 3). Shortly there-

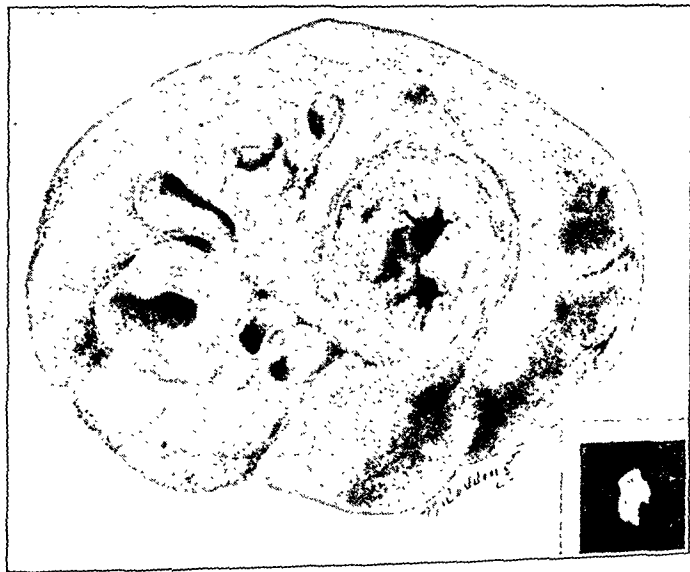


Fig. 5.—Heart of dog X15. The leaflets of the mitral valve are puckered and contracted, and an obvious defect is apparent in the lateral segment. The insert shows the section that was removed at operation.

after the respirations became labored and gasping; a right ventricular puncture was attempted to relieve pulmonary congestion, but it was unsuccessful, and death occurred four hours after operation.

*Autopsy.*—About 50 cc. of liquid blood was found in each pleural cavity. The wound in the myocardium was solid; the coronary vessels were uninjured. There was marked congestion of the right auricle and ventricle. The lungs showed early pulmonary edema. There was no gross evidence of acute congestion of the liver or spleen.

After removal of the heart, the roof of the left auricle was excised and the mitral valve was examined from above. The leaflets were thickened and fibrosed, and a moderately large defect was apparent in the lateral segment (fig. 5). Death was attributed to acute cardiac failure.

*Comment.*—With the single exception of the consumption of oxygen per minute, the results in this case (table 3) were exactly comparable to those found in experiment 3.

EXPERIMENT 6.—Dog X25 (control), a male, mongrel bull terrier, weighing 17.6 Kg., was trained to lie quietly on the table while two sets of physiologic studies were carried out (table 4).

Partial resection of the mitral valve was performed on Dec. 17, 1930. Two segments of normal valve were removed with the cardiovalvulotome. There was no hemorrhage. The wound was closed in layers with silk. A systolic murmur was audible immediately after operation. Physiologic studies were repeated at

TABLE 4.—*Observations on the Normal Control Dog, X25 (a Mongrel Bull Terrier, Weighing 17.6 Kg.) \**

Date	Pulse Rate per Min.	Blood Pressure, Mm. Hg	Oxygen Consumption, Cc. per Min.	Arterial Oxygen	Venous Oxygen	Oxygen Utilization, per Cent by Vol.	Cardiac Output, Cc. per Min.	Stroke Output, Cc. per Beat	Comment
12/11/30	69	110/70	155.14	18.93	14.47	4.46	3,475	51.1	
12/15/30	72	90/50	155.36	18.76	14.28	4.48	3,465	48.1	Cardiac sounds normal
12/17/30 11:00 a.m.		Operation: Partial resection of normal mitral valve							
12/17/30 2:00 p.m.	116	70/50	132.43	19.47	13.72	5.75	2,305	19.8	Loud, blowing systolic murmur
12/17/30 8:30 p.m.	116	70/50	121.08	19.18	13.53	5.65	2,145	18.5	
12/18/30 11:30 p.m.	108	130/90	116.14	17.93	12.45	5.48	2,120	19.6	
12/19/30	108	150/110	134.32	16.34	10.41	5.93	3,365	20.9	
12/20/30	96	.....	156.66	15.37	10.56	4.84	3,235	33.7	
12/22/30	96	135/100	149.86	16.34	11.26	5.08	2,950	30.7	
12/24/30	96	140/100	166.14	16.47	10.62	5.85	2,845	29.6	
12/29/30	90	130/90	161.48	16.94	11.68	5.26	3,070	34.1	Murmur unchanged
12/29/30	Killed. Autopsy: well marked mitral regurgitation; no congestion of lungs or liver; slight cardiac enlargement								

\* The postoperative determinations show similar but much less radical changes than those observed after the excision of a segment from the valve of an animal with stenosis.

intervals during the next twelve days (recorded in detail in table 4). The animal was then killed.

*Autopsy.*—The wound was firmly healed. There was no fluid in either pleural cavity. Examination of the mitral valve showed a defect in both the lateral and aortic segments; otherwise it was normal. The lungs, liver and spleen were normal.

*Comment.*—After removing a segment of this normal valve, an immediate decrease in cardiac output per minute and per beat was found. The change was much less marked, however, than the abrupt alteration that occurred after partial resection of a stenotic valve. On the second postoperative day the minute output had returned to normal, although the stroke output was still low. Only very slight changes were noted in the content of oxygen in arterial and venous blood, and the utilization of oxygen remained essentially the same throughout.

## COMMENT

All previous discussions regarding the surgical treatment of mitral stenosis have been prefaced by the assumption that mitral insufficiency is a far less serious condition than mitral stenosis. Ample clinical data are at hand to support this theory, and on the basis of this evidence nine patients with mitral stenosis have been subjected to valvulotomy or partial valvectomy. The mechanical technic of the operation has been accomplished successfully and regurgitation has been created, but the patients have died. In other words, the abrupt alteration in the circulatory mechanics that occurs with the sudden operative conversion of mitral stenosis into insufficiency is by no means comparable to the gradual compensatory adjustment that follows the slow development of a similar lesion by pathologic processes. The experimental work herein recorded has been offered in support of this contention.

All five dogs with experimental mitral stenosis died after the removal of a portion of the obstructing valve. Postmortem examination of each animal disclosed tremendous dilatation and engorgement of the right side of the heart, acute pulmonary congestion and edema, pleural effusion, acute and chronic congestion of the liver with central necrosis<sup>11</sup> and, in one case, ascites.

A consideration of the physiologic studies, as they are presented in tabular form, reveals certain interesting and consistent alterations in the circulation of three animals after the transformation of mitral stenosis into insufficiency. Analysis of these results throws some light on the physiology of acute cardiac decompensation and the circulatory derangements that terminate in death. The series of observations on dog X12 is most instructive, for the studies were repeated at intervals during the first week after operation. They present more gradual changes than do the observations on the remaining two animals, both of which died so early in the postoperative course that only one series of observations could be carried out. The determinations on all three animals, however, are consistent throughout and disclose the following facts:

A marked increase in pulse rate occurred immediately after the excision of a segment of the stenotic valve.

The blood pressure fell.

The consumption of oxygen was decreased in one instance and increased in two. (This is the only variation in all the postoperative results.)

The oxygen content of arterial blood was diminished to a remarkable degree.

The decrease in venous oxygen was even more striking.

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11. Dr. George Mackenzie and Dr. Ruben Schultz assisted in interpreting the histologic sections.

The utilization of oxygen, or the difference between the content of oxygen in arterial and that in venous blood, was greatly increased.

The cardiac output per minute was reduced. In dog X11 this decrease amounted to 73 per cent of the average preoperative level.

The stroke output was diminished to an even greater degree than the total output.

Similar but much less radical changes were observed after the production of mitral insufficiency in the normal control dog, X25, in which circulatory readjustment was rapid and adequate to sustain life.

From these results, one must conclude that although mitral regurgitation may be created in normal dogs without clinical evidence of decompensation, the abrupt conversion of experimental chronic mitral stenosis into insufficiency produces such sudden and radical alterations in the mechanics of the circulation that cardiac decompensation and death ensue.

The canine lesion was comparable in its gross pathologic aspects to mitral stenosis of rheumatic origin in man. The instrument and the operative technic were similar to those which have been employed on human beings. It seems justifiable to assume, therefore, that the physiologic alterations in the circulation that account for death after partial valvulectomy on animals may explain the same result following a similar procedure on man.

Could mitral stenosis be relieved more gradually, either by repeated excision of tiny fragments of the valve, by multiple incisions into the obstructing segments or by dilatation of the stenotic orifice, the results might be more satisfactory. The only two cases in which the operation was not succeeded immediately by a fatal outcome were Cutler's first case, in which simple incision into the segments of the valve was performed, and Souttar's case, in which the mitral orifice was dilated with the finger. In both of these procedures only a slight change was produced in the size of the orifice. Souttar's patient is living five years after operation and presents the appearance observed in a well compensated case of mitral stenosis.<sup>12</sup>

#### SUMMARY AND CONCLUSION

The experimental counterpart of chronic mitral stenosis in man was produced in five dogs by electrocoagulation of the mitral valve followed by intravenous inoculation with cultures of *Streptococcus viridans*. Partial valvulectomy was performed subsequently with the cardiovalvulotome. The animals died within from three hours to nine days after operation. Both the physiologic and pathologic data presented support the contention that death was due to acute cardiac failure attendant on

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12. Souttar, H. S.: Personal communication to the author.

the abrupt and radical conversion of stenosis into stenosis with insufficiency.

Although the number of these experiments is small, the results suggest that the creation of a large defect in the scarred and contracted orifice of mitral stenosis is an extremely hazardous procedure which may lead to acute cardiac decompensation and death. Could this transformation to insufficiency be carried out more gradually by less radical or repeated operative maneuvers, the outcome might be more satisfactory.

# RESPIRATORY PARALYSIS IN SPINAL ANESTHESIA

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Opinions as to the field and indications for spinal anesthesia differ sharply. Published statistics are favorable, but much first-class surgical opinion is adverse to this method, for many individual results have been unfavorable. The prevailing confusion seems due to our failure to divide a large subject into its constituent problems and subject each of these to adequate investigation. The most serious problem at the moment concerns high spinal anesthesia. Is there danger that respiratory paralysis will supervene when the anesthesia extends up to the arms, neck and face, or is such a fear foolish and the pains taken to avoid it unnecessary? The present communication is an effort to throw light on this question.

Universal experience has accumulated a considerable mass of pertinent data. Procaine hydrochloride introduced into the subarachnoid space, or brought into contact with motor nerve fibers more distally, produces paralysis of ordinary striated muscle. Experience with spinal and local anesthesia has discovered no motor fibers that are immune. All nerve fibers, both sensory and motor, have their conductivity interrupted by procaine hydrochloride.

The investigations of the physiologists have given the same answer. There is a very extensive literature concerned with the effect of anesthetics and narcotics on nerve fibers and nerve centers. In general, the centers are much more susceptible than the fibers, as every general anesthesia shows, for motor nerves are still capable of stimulation, even when the patient is adequately or even dangerously under the influence of the anesthetic. Moreover, all nerve fibers are influenced by anesthetics in the same way. This is what was to be expected, of course, for all nerve fibers can transmit impulses in both directions, and so far as we know, are similar in structure. The slight differences in susceptibility between nerve fibers of different functions appear to depend on nothing except their different size. Thus the pain fibers yield to the action of cocaine slightly more readily than temperature fibers, and the tempera-



ture fibers more readily than the proprioceptive and motor fibers, this being due simply to the small size of the pain fibers and the increasing sizes of the others. Pressure interrupts the conductivity of the different fibers in the reverse order.<sup>1</sup>

The action of procaine hydrochloride has been investigated by the pharmacologists in great detail. Solutions as weak as 0.25 per cent interrupt the conductivity of the motor fibers in the sciatic nerve of a frog, within twenty minutes. A 1 per cent solution accomplishes this result in five minutes.<sup>2</sup> Results reported here indicate that the motor nerves of a cat are not substantially different in their susceptibility.

A consideration of the literature would lead to the conclusion that a spinal anesthesia that involves the cervical region must be dangerous, for the phrenic nerve is made up of fibers that leave the cord in the fourth anterior cervical root, with varying contributions from the third and the fifth. Operations involving the arms, neck and face require the application of an anesthetic solution to the posterior roots in precisely this region. There is, however, some experimental evidence and much more clinical experience that is at variance with this conclusion. Labat and Leriche have contended for some time that respiratory paralysis does not occur in high spinal anesthetics, and that the deaths so interpreted are really due to cerebral anemia. Koster and Kasman published an impressive article in which this opinion is supported by an extensive clinical experience as well as by a certain amount of experimental work.<sup>3</sup>

A factor that may help explain the discrepancy between the results of the physiologists and the surgeons is that local anesthetics vary greatly in their capacity to penetrate to nerve fibers and nerve cells not lying on the surface and not bathed intimately by the anesthetic solution. Procaine hydrochloride penetrates very poorly, indeed, and this may serve to protect important fibers and centers from its action. Moreover, anatomic relationships or currents in the cerebrospinal fluid may keep the anesthetic solution away from certain areas while permitting access to others. However, safety, depending on anatomic relationships which presumably vary somewhat from patient to patient, or on currents in the cerebrospinal fluid which are probably not always the same in direction and intensity, seems somewhat dubious. At the very least, it requires investigation, so that one may have some idea of where the limits of safety lie.

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1. Gerard, R. W.: Nerve Conduction in Relation to Nerve Structure, *Quart. Rev. Biol.* 6:59 (March) 1931. This not only is an excellent review of the whole subject, but gives a good bibliography, which makes possible a detailed study of any point of special interest.

2. Sollmann, Torald: *J. Pharmacol. & Exper. Therap.* 10:379, 1917.

3. Koster and Kasman: *Surg., Gynec. & Obst.* 49:617 (Dec.) 1929.

## EXPERIMENTAL WORK

Cats were chosen for this investigation, and no effort was made to investigate drugs other than procaine hydrochloride. The first experiments were concerned with general principles.

**SERIES A.**—The sciatic nerve was isolated. The muscles were arranged with or without sutures so that 1 or 2 cm. of the nerve could be immersed in procaine hydrochloride in situ. In this way it was possible to test the conductivity of the nerve before applying the solution, demonstrate blocking by the solution, wash out the procaine hydrochloride with physiologic solution of sodium chloride and test again for restored conductivity. Four nerves were prepared in two cats.

Three per cent procaine hydrochloride dissolved in physiologic solution of sodium chloride produced complete block in twenty minutes; 2 per cent, in 20 minutes, and 1 per cent produced almost complete block in thirty minutes.

**SERIES B.**—The phrenic nerves were isolated in the neck. They were prepared as in series A. Four nerves were prepared in two cats. Each was tested with 1 per cent procaine hydrochloride. One nerve was completely blocked in twenty minutes, one in twenty-five minutes, one in ten minutes and one in forty minutes. Exposure was somewhat imperfect in the last case.

The phrenic is a more delicate nerve than the sciatic, and its individual fibers are more easily reached by the surrounding solution. If brought into intimate contact with the individual nerve fibers, a very weak solution of procaine will block all conductivity. Illustrative of this, though originally performed with another object in view, were some infiltrations of the spinal cord itself.

**SERIES C.**—The spinal cord was edematized at the level of the second to the third roots with physiologic solution of sodium chloride. The solution was introduced through a very fine hypodermic needle. Three cats were used. No effect on the respiration was observed in any case. The cord was edematized with 2 per cent procaine hydrochloride. Respiration stopped in twenty-seven minutes. With 1 per cent procaine hydrochloride, it stopped in fourteen minutes; with 0.5 per cent, in twenty-nine minutes, and with 0.25 per cent, in seven minutes. The edematization was more carefully performed in the last experiment, and evidently the cord was divided into smaller fiber bundles by the infiltrating fluid.

Illustrative of the marked incapacity of procaine hydrochloride to penetrate to structures lying below the surface were some experiments in which the fourth ventricle was flooded with the solution. These experiments also had a different object when they were performed.

**SERIES D.**—Four cats were used. The medulla and cerebellum were widely exposed. The surrounding soft parts were arranged to make possible a lake of fluid over the exposed area. The area maintained was covered with procaine hydrochloride. The solution was frequently renewed to avoid dilution with tissue fluids.

*Cat 1.*—The cerebellum was unretracted. The area was laked with 1 per cent procaine hydrochloride for sixty-seven minutes, with 1.5 per cent for thirty minutes, with 2 per cent for thirty minutes and with 4 per cent for twenty minutes. At this point respirations stopped, i.e., after one hundred and seventy-seven minutes.

*Cat 2.*—The same exposure was obtained as in cat 1. The cerebellum was retracted, and the floor of the fourth ventricle was well exposed. The area was laked with 1 per cent procaine hydrochloride for thirty-three minutes, 1.5 per cent for twenty-six minutes and 2 per cent for thirty-one minutes. At this point respirations stopped after ninety minutes.

*Cat 3.*—The same procedures were carried out. One and one-half per cent procaine hydrochloride was used for thirty-one minutes and 2 per cent for twelve minutes. At this point respirations stopped, i.e., after forty-three minutes.

*Cat 4.*—The same procedure was carried out as on cats two and three. One and one-half per cent procaine hydrochloride was used for thirty minutes and 2 per cent for forty-six minutes. Respirations stopped after seventy-six minutes.

It is true that the respiratory center has not been exactly located and that in a sense it is a physiologic rather than an anatomic conception. Nevertheless, there is very convincing evidence that it lies in the floor of the fourth ventricle, and close to the surface, so that the experiments in this series stand as a good demonstration of the exceedingly limited capacity of procaine hydrochloride to penetrate to structures even a little removed from the surface actually bathed by the anesthetic solution.

To ascertain the susceptibility of the anterior cervical roots, three series of experiments were performed.

**SERIES E.**—Two cats were used. The dorsal aspect of the cervical cord was exposed by removing the vertebral arches from the second cervical to the seventh. Wide removal of the bone was done laterally. The dura was divided in the mid-line, incised transversely at each end, and retracted widely. The posterior roots were exposed. The soft parts were arranged to make possible a lake of solution over the exposed area.

*Cat 1.*—The exposed cord was laked with 1 per cent procaine hydrochloride for two hours. No effect on the respiration was observed. The cat was used for other purposes.

*Cat 2.*—The exposed cord was laked with 4 per cent procaine hydrochloride for three and one-half hours. There was no effect on the respiration. The cat was used for other purposes.

It was decided that with this exposure, the anterior roots were not being reached.

**SERIES F.**—Eleven cats were used. The exposure and general procedure was the same as in series E. In some of these cats the anesthetic solution was introduced between the anterior surface of the cord and the dura by means of a fine glass dropper which was introduced along the side of the cord through the dentate ligament. In others, a ureteral catheter was introduced and left lying with its tip in the space between the anterior surface of the cord and the dura. After introducing the catheter, the cat was watched for several minutes to be sure that the introduction of such a gross foreign body was not of itself disturbing the respiratory movements.

Various strengths of procaine hydrochloride were introduced through the tube or catheter in quantity sufficient to lake the entire exposed area. The solutions were renewed frequently. The time that elapsed before respiration stopped varied greatly. It seemed to have little relation to the strength of the solutions introduced. For the eleven cats the periods elapsing before respiration stopped ran

as follows: forty-nine minutes, seventy-five minutes, forty-five minutes, one hundred and two minutes, one hundred and twelve minutes, seventy-seven minutes, thirty-seven minutes, eighty-two minutes, fifty-two minutes, one hundred and seventeen minutes and fifty-five minutes, an average of seventy-three minutes. It was evident that even when introduced in this way the solution gained a capricious and uncertain access to the anterior roots, and that we were measuring not the susceptibility of the roots but rather the time which it took for the solution to gain access to them.

**SERIES G.**—Two cats were used. The procedure was the same as in preceding series except that the exposure was extended laterally till well over half of the bony tube surrounding the cord was removed. The dura was opened very widely. Series of very coarse sutures were inserted into the cord longitudinally and carried up over a delicate glass rod which stretched from one brim of the wound to the other. The rod was raised by insertion of bits of cotton or gauze under its ends, until the sutures began to tear. In this way the cord was pulled up till its cross-section was more or less triangular. The preparation was regarded as satisfactory only if physiologic solution of sodium chloride could be washed from side to side between the anterior surface of the cord and the dura. The cats were watched for a number of minutes to be sure that the mechanical insults incident to this experiment had not disturbed the respiration.

*Cat 1.*—The procedure was as previously described. One per cent procaine hydrochloride was applied. It was found impossible to wash the solution through. The glass rod was readjusted. The solution now washed through well. Respiration stopped twenty-five minutes from the time of the first application, and seven minutes from the time that readjustment made a satisfactory access possible.

*Cat 2.*—The preparation was the same as for cat 1. One per cent procaine hydrochloride was applied. It washed through well. Respiration stopped in seventeen minutes.

It is evident from these experiments that the motor nerve fibers that run to the diaphragm are just as susceptible to the action of procaine hydrochloride when acted on in the anterior cervical roots, as when exposed to the solutions lower down in the phrenic nerve.

All the foregoing experiments may be regarded as demonstrating over again what we knew already, or at least what we might have concluded from the literature, i. e., that no nerve fibers, either sensory or motor, enjoy any immunity from the action of procaine hydrochloride, and that for practical purposes there is no difference between the sensory and the motor fibers. They demonstrate another thing also, namely, that it is a matter of surprising difficulty for the anesthetic solution to gain access to the anterior cervical roots. Devising and setting up experimental conditions which made that access possible was a matter of considerable difficulty. There are other ways of demonstrating this difficulty.

**SERIES H.**—Three cats were used. The needle was introduced into the subarachnoid space between the base of the skull and the first vertebral arch. Ten drops of cerebrospinal fluid were allowed to escape. One-fourth cubic centimeter of solution was then introduced.

*Cat 1.*—One-fourth cubic centimeter of 1 per cent procaine hydrochloride was introduced. Paralysis of the fore limbs was almost complete; it lasted forty minutes. Anesthesia of the body was complete except for some areas on the face. This lasted about forty minutes. Respiration was unaffected. The cat recovered.

*Cat 2.*—One-fourth cubic centimeter of 1 per cent procaine hydrochloride was introduced. Paralysis of the fore legs lasted fifteen minutes. Anesthesia of the entire body lasted thirty minutes. Respiration was unaffected. The cat recovered.

*Cat 3.*—In cats 1 and 2 the needle was introduced under light ether anesthesia. The ether was stopped as soon as the solution was introduced. In this cat the needle was introduced with no anesthetic of any sort. One-fourth cubic centimeter of 5.5 per cent of procaine hydrochloride (isotonic solution) was introduced as indicated. Following this dose, the body was absolutely anesthetic except for scattered areas on the tail. The corneas were anesthetic. All use of fore and hind limbs was impossible. The fore limbs were almost completely flaccid. Respirations were rapid but not shallow or otherwise affected. Anesthesia persisted for nearly an hour; the paralysis for about half that time. The animal recovered.

Such extreme involvement of the fore limbs with respiratory movements almost or quite normal is a finding that we are not able to explain. This protection of the respiratory nerves is not absolute, however.

**SERIES I.**—Four cats were used. The solutions were introduced as in the preceding series, but were weighted so that they would sink to the lowest available point.

*Cat 1.*—Five per cent procaine hydrochloride was weighted with 5 per cent iron and ammonium citrate, U.S.P., and 5 per cent sodium ferrocyanide. Anesthesia of the body was apparently complete. No sensitive spot was found. Paralysis of the limbs was apparently complete. Respirations stopped in fifteen minutes. The cord was hardened in situ with acid formaldehyde and dissected out. Prussian blue coloring was found over the whole anterior cervical region. Posteriorly, the blue coloring extended well into the thoracic region.

*Cat 2.*—One-fourth cubic centimeter of a 5.5 per cent procaine hydrochloride in 10 per cent cane sugar solution was used. Anesthesia was complete except for slight reaction to stimulation of right cornea. Some tone was discernible in the fore limbs. The respiration rapidly became shallow and seemed about to stop. Improvement was noted after thirty minutes. The cat recovered.

*Cat 3.*—Cat 3 was treated the same as number 2 except that the cane sugar was increased to 15 per cent. Respiration stopped after five minutes.

*Cat 4.*—One per cent procaine hydrochloride solution was used in 15 per cent cane sugar. Respirations stopped in three minutes. The heart beat persisted for three minutes longer.

If these cats died because the weight of the solution carried it down to the anterior roots where the motor fibers destined for the diaphragm were blocked, turning the animal on its back immediately after the solution is introduced ought to change the result.

**SERIES J.**—Three cats were used. The same procedure was used as in the preceding series except that the cat was turned on its back immediately after the introduction of the solution and kept there.

*Cat 1.*—One-fourth cubic centimeter of 5 per cent procaine hydrochloride was weighted with 5 per cent iron and ammonium citrate and 5 per cent sodium ferrocyanide. Anesthesia of the body was complete. The right fore limb was largely paralyzed. The left fore limb was much less affected. Respiration was unaffected. Recovery occurred after from thirty minutes to one hour.

*Cat 2.*—The same procedure was employed as on cat 1. Respiration was severely affected, but the cat recovered. Anesthesia of the body was complete.

*Cat 3.*—This cat was treated the same as cat 2. Respirations stopped in about ten minutes.

It was obvious from these experiments that weighted solutions found their way to the anterior roots much more readily than the simple unweighted ones, and moreover that whatever the factors may be that afford protection to the anterior cervical roots, they are by no means uniform and certain in their action. Experimental procedures that result in recovery in one case are fatal in another.

#### CONCLUSIONS

1. Motor nerve fibers enjoy no immunity from the action of procaine hydrochloride; differences between the susceptibility of motor and sensory fibers are insignificant.

2. The motor fibers leaving the cord in the third, fourth and fifth anterior cervical roots, and running through the phrenic nerve to carry motor impulses to the diaphragm, show the same susceptibility to procaine hydrochloride as other motor nerve fibers.

3. Freedom from respiratory paralysis in spinal anesthetics that involve the cervical region must be due to some factors that protect the anterior roots from contact with the anesthetic solution.

4. In the cat these protecting factors are capricious and uncertain in their action.

This work was done under the supervision of Dr. Dean Lewis, and under the guidance of Dr. Lee, director of the Hunterian Laboratory, the staff of which gave their technical assistance.

# ROENTGENOGRAPHIC MANIFESTATIONS OF INTESTINAL OBSTRUCTION

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( The treatment for intestinal obstruction has in the majority of cases been relegated almost entirely to the surgeon, the conservative measures of medical treatment having been more or less discarded. In spite of this fact, and even though surgical methods have improved in the last three decades, the mortality rates remain alarmingly high. The experience of recent years has emphasized the importance of an early diagnosis in intestinal obstruction if surgical intervention is to be a life-saving measure. Most writers, therefore, agree that the one way of reducing the mortality rates is to shorten the time interval between the onset of symptoms and the establishing of a definite diagnosis. Statistics quoted by various writers demonstrate this quite strikingly. Miller,<sup>1</sup> in a study of a series of cases, showed that the death rate almost doubled between the twelve and the twenty-four hour intervals. His total mortality was 60.9 per cent in 343 cases. Brill<sup>2</sup> reported no deaths in those cases in which operation was done within twelve hours, whereas between the twelve to the twenty-four and the twenty-four to the forty-eight hour periods his mortality increased approximately five times. North<sup>3</sup> reported statistics to show that the mortality at operation, done in less than six hours after the onset of symptoms was 9 per cent as compared with 23 per cent between twenty-five and forty-eight hours. Tuttle<sup>4</sup> had no deaths when operation was performed in less than six hours after symptoms appeared but showed a rise of from 4 to 15 per cent when the time interval was between twelve and twenty-four hours. Eliason and North<sup>5</sup> quoted statistics that show a decrease of only 12 per cent in their series of 1928 as compared with Deaver and Ross in

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1 Miller, C. J.: A Study of 343 Surgical Cases of Intestinal Obstruction, *Ann. Surg.* **89**:91, 1929.

2. Brill, S.: Mortality of Intestinal Obstruction, *Ann. Surg.* **89**:541, 1929.

3. North, John Paul: Acute Intestinal Obstruction, *Internat. Clin.* **3**:206, 1929.

4. Tuttle, H. W.: The Mortality of Intestinal Obstruction, *Boston M. & S. J.* **192**:791, 1925.

5. Eliason and North, quoted by North (footnote 3).

their statistics of 1915. At the Presbyterian Hospital our statistics show a 41.8 per cent mortality in the last three years, including all cases of acute and chronic obstruction in which operation had been done, regardless of the time factor or the cause.) Table 1 records those cases in which roentgen examination was used as an aid in diagnosis. In this instance, the death rate is lower than the general average. We would call attention to the decrease in the death rate in those cases in which operation was done ninety-six hours following the onset of symptoms. This is due to the fact that about 80 per cent of the cases of chronic obstruction fall in this group. The patients were more apt to recover from the immediate operative procedure, but succumbed later to the underlying cause, which in most cases was a malignant growth.

(The knowledge gained from the roentgenographic examination of the abdomen has been stressed as one of the main factors in aiding an

TABLE 1.—*Mortality in Cases in Which X-Rays Were Used in Diagnosis*

Hours from Onset of Symptoms to Operation	Number of Cases	Deaths	Percentage
Under 12.....	4	0	0
13 to 24.....	12	4	33.3
25 to 48.....	8	3	37.5
49 to 96.....	8	5	62.5
Over 96.....	15	5	33.3
Total.....	47	17	36
Total cases of obstruction.....			91
Total cases of obstruction in which the x-rays were used in diagnosis.....			55
Total cases of obstruction in which the x-rays were used in diagnosis and no operation done			7
Total cases of obstruction in which the x-rays were used in diagnosis and operation done..			48

early diagnosis, for if a sharper diagnostic eye can be developed in viewing the abdominal films in these cases, the problem has been aided considerably.) It is with this idea in mind that some observations on the roentgen diagnosis of intestinal obstruction are presented. We propose to deal entirely with the diagnostic problem so far as the roentgenographic evidence is concerned.

#### LITERATURE

(The diagnosis of intestinal obstruction by means of the roentgen rays is not a new procedure. The recognition of the positive densities created by the gas-filled loops of bowel was described as early as 1911, when Schwarz<sup>6</sup> advocated the administration of a small amount of barium sulphate suspension for the production of fluid levels and emphasized that the erect position of the patient be used in order that the fluid levels might be demonstrated. Assmann,<sup>7</sup> in 1913, reported five cases proved

6. Schwarz, Gottwald: Die Erkennung der tieferen Dünndarmstenose mittels des Röntgenverfahrens, Wien. klin. Wchnschr. **24**:1386, 1911.

7. Assmann, H.: Zur Röntgendiagnostik der Dünndarmstenosen, Deutsche Ztschr. f. Nervenhe. **1**:47, 1913.



at post mortem to be obstructions which had shown both gas and fluid levels by roentgen examination. Case<sup>8</sup> did the pioneer work along this line in America, beginning his work in 1910, and later in 1915 published a paper stressing the characteristic parallel loops of distended bowel. Later, particularly in his publication of 1927, he added the finer points of diagnosis such as the "herring bone" appearance of the mildly distended loops of bowel as compared to the "ladder effect" caused by the greatly distended loops. He also described the fluid levels discernible in the various positions. Meyer and Brams<sup>9</sup> and Rabwin<sup>10</sup> emphasized the gas shadows but did not stress fluid levels. Kalbfleisch<sup>11</sup> expressed the opinion that distended loops of bowel only suggest obstruction, whereas the presence of fluid levels is definite confirmatory evidence. Bensaude and Guénaux<sup>12</sup> described fluid levels in the ascending colon in the presence of obstruction in the distal portion of the colon. Other writers prominent in emphasizing the value of roentgen examination of the abdomen in ileus are Guillaume,<sup>13</sup> Martens,<sup>14</sup> Hintze,<sup>15</sup> Kloiber,<sup>16</sup> Davis,<sup>17</sup> Ochsner and Granger,<sup>18</sup> Brown,<sup>19</sup> Weil<sup>20</sup> and Milhaud.<sup>21</sup>

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8. Case, J. T.: Roentgenological Aid in the Diagnosis of Ileus, *Am. J. Roentgenol.* **19**:413, 1927; The Value of the Roentgen Examination in the Early Diagnosis of Post-Operative Ileus, *Ann. Surg.* **79**:715, 1924; Roentgen Studies After Gastric and Intestinal Operations, *J. A. M. A.* **65**:1628 (Nov. 6) 1915.

9. Meyer, K. A., and Brams, W. A.: Clinical Study of Acute Intestinal Obstruction, *Illinois M. J.* **51**:42, 1927.

10. Rabwin, M. H.: The Roentgen-Ray Diagnosis of Acute Intestinal Obstruction, *Am. J. Surg.* **7**:656, 1929.

11. Kalbfleisch, William K.: The Diagnosis of Intestinal Obstruction by Roentgen Ray, *Am. J. M. Sc.* **174**:500, 1927.

12. Bensaude, R., and Guénaux, G.: Le radiodiagnostic des stenoses du gros intestin, *Paris méd.* **7**:467, 1917.

13. Guillaume, A. C.: A propos du diagnostic de l'occlusion intestinale aiguë (l'examen radiologique de l'ileus), *Presse méd.* **30**:3, 1922.

14. Martens, M.: Ileus im Röntgenbilde, *Med. Klin.* **24**:1417, 1928.

15. Hintze, Arthur: Allgemeine topische und Ursachendiagnosen des Ileus durch die Röntgenuntersuchung, *Med. Klin.* **24**:1547, 1928.

16. Kloiber, Hans: Die Roentgendiagnose des Ileus ohne Kontrastmittel, *Arch. f. klin. Chir.* **112**:513, 1919.

17. Davis, K. S.: A Valuable Roentgenographic Aid in Diagnosis of Intestinal Obstruction, *Am. J. Roentgenol.* **17**:543, 1927.

18. Ochsner, A., and Granger, A.: Roentgen Diagnosis of Ileus, *Ann. Surg.* **92**:947, 1930.

19. Brown, Samuel: Gastro-Intestinal Obstructions, *Radiology* **15**:364, 1930.

20. Weil, A.: Ueber die Röntgendiagnostische Bedeutung normaler und abnormaler Gasansammlung im Abdomen, *Fortschr. a. d. Geb. d. Röntgenstrahlen* **24**:1, 1916.

21. Milhaud: Stenoses de l'intestin grêle radiographiques, *Lyon méd.* **130**:854, 1921.

Wangensteen and Lynch<sup>22</sup> were apparently the first to study the roentgen manifestations in experimentally produced ileus. They produced mechanical obstruction in dogs and observed its course roentgenographically. They found that gas in the obstructed intestine could be detected on the roentgen film in from four to five hours, and that clinical distention was not evident until many hours later. Fluid levels could not be demonstrated with any degree of regularity unless fluid was given either intravenously or by hypodermoclysis. Later, Wangensteen and his co-workers<sup>23</sup> produced strangulation in a segment of intestine and found that the roentgen evidence of obstruction was not as definite as in simple obstruction.)

#### PHYSIOLOGY

Although Case,<sup>24</sup> Wangensteen and Lynch<sup>22</sup> and Weil<sup>20</sup> are inclined to believe that gas in sufficient quantities to be recognizable on the roentgen film is never seen normally in the small intestine, we find, from our own observations, that small amounts are occasionally seen. The most frequent location of these apparently innocent gas shadows is either the duodenum or distal portion of the ileum. Its presence in the first instance may be accounted for by an excessive amount of gas in the stomach, while its presence in the distal portion of the small intestine can be explained on the frequently found incompetency of Bauhin's valve. Again, in diseases of the small bowel in which the normal physiology is impaired to the extent of a slight decrease in motility, there may be small amounts visible that do not denote an actual obstruction of surgical importance. The differentiation in these instances from cases of obstruction can readily be made since there is no dilatation of the bowel lumen above the usually observed 2.5 to 3 cm. width, and the shadows are only transient. Furthermore, clinical evidence is absent, the observation generally being incidental. The foregoing observations apply to adults only, since distended small intestinal loops are commonly seen in infants up to about 2 years of age in which there is obviously no obstruction clinically.

Kantor and Marks,<sup>25</sup> in discussing the origin of intestinal gases, stated that they are derived from two sources, namely, from the atmos-

22. Wangensteen, O. W., and Lynch, F. W.: Evaluation of X-Ray Evidence as a Criterion of Intestinal Obstruction, *Proc. Soc. Exper. Biol. & Med.* **27**:674, 1930.

23. Wangensteen, O. H.; Goehl, R. O.; Lynch, F. W., and Borman, C.: Evaluation of X-Ray Evidence as a Criterion of Strangulation Obstruction, *Proc. Soc. Exper. Biol. & Med.* **27**:952, 1930.

24. Case (footnote 8, first reference).

25. Kantor, John L., and Marks, J. A.: A Study of Intestinal Flatulence, *Ann. Int. Med.* **3**:403, 1929.

pheric air and from food stuffs. Atmospheric air is swallowed during eating and drinking and the greater part of it is quickly eliminated by belching. The nitrogen which composes 80 per cent of the volume is not absorbed by the blood stream and the oxygen (20 per cent) is only moderately absorbable. An enormous amount of gas originates from the food stuffs during digestion in the upper part and from the possible bacterial decomposition of sugars in the lower part of the small intestine. Most of the gas coming from the food is absorbed by the blood stream and exhaled through the expired air.

Zuntz and Tacke<sup>26</sup> demonstrated that, under normal conditions, intestinal gas is eliminated mainly by way of the blood stream, only a very small portion being expelled.

In intestinal obstruction the normal pathways of elimination are either partially or completely blocked. Not only is the mechanism of expulsion impaired but, as Ochsner and Granger<sup>18</sup> point out, absorption into the blood stream is interfered with as well, for there is always some interference with the blood supply of the intestine, although it may be at times entirely intramural. This is due to the pressure produced by the intestinal contents, the expulsion of which has been retarded by a mechanical or paralytic obstruction as the case may be.

Coincident with the foregoing processes, there is an active diffusion of gas and secretion of fluid from the blood stream into the bowel lumen. McIver, Redfield and Benedict<sup>27</sup> and McIver, Benedict and Cline<sup>28</sup> explained that in meteorism gas is diffused from the blood into the intestine. Furthermore, Morton and Sullivan<sup>29</sup> showed experimentally that the secretion of fluid into the bowel is greatly increased as the duration of the obstruction increases. Müller<sup>30</sup> observed experimentally a marked increase in the secretion of fluid into the intestine in paralytic ileus.

Thus, to summarize, it can be stated that with the stagnation of the normal intestinal content and its decomposition, with the impairment of absorption and with the increase in the secretory power of the intestine, there is produced the gas-distended bowel containing fluid proximal to the point of obstruction.

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26. Zuntz and Tacke: *Deutsche med. Wchnschr.* **10**:717, 1884.

27. McIver, M. H.; Redfield, N. C., and Benedict, E. B.: *Am. J. Physiol.* **76**:92, 1926.

28. McIver, M. H.; Benedict, E. B., and Cline, J. W.: *Post-Operative Gaseous Distention of Intestine*, *Arch. Surg.* **13**:588 (Sept.) 1926.

29. Morton, J. J., and Sullivan, W. C.: *A Comparison Between Simultaneous Equalized Closed Obstruction of the Duodenum and the Ileum*, *Arch. Surg.* **21**:531 (Sept.) 1930.

30. Müller, E. F.: *Ueber den paralytischen Ileus*, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **41**:417, 1929.

## EXPERIMENTAL WORK

Experimental ileus was produced in thirteen dogs by procedures similar to those used by Wangenstein and Lynch.<sup>22</sup> In nine of the experiments, obstruction was produced mechanically and in four paralytic ileus was produced. All animals were operated on under ether narcosis and strictly sterile technic. In the first two of the mechanically obstructed group, the small intestine was occluded in two stages; the abdomen was opened, a strand of umbilical tape was loosely placed around the intestine close to the ileocecal junction and the ends brought out through a stab wound, the obstruction being completed forty-eight hours later without anesthesia by tying the ends taut over a button. In experiments 6, 9 and 10, the intestine was severed and the divided ends were inverted, while in the remaining four the intestine was ligated with umbilical tape at the desired level. In six animals the obstruction was established close to the ileocecal junction, and in three approximately midway between the ligament of Treitz and the cecum.

Paralytic ileus was successfully produced in four animals by the following procedure: The lower half of the small intestine was painted with tincture of iodine, the appendix was ligated at its base and its blood supply severed, after which it was opened in its entire length and its contents spread diffusely throughout the peritoneal cavity. The injection of 20 cc. of a 2 per cent solution of iodine into the peritoneal cavity as described by Markowitz and Campbell<sup>31</sup> was used in one animal without results. The intraperitoneal injection of 4 Gm. of fresh feces in 20 cc. of saline as used by Steinberg and Goldblaut<sup>32</sup> was also unsuccessful.

Postmortem examinations were done on all the animals after the desired series of roentgenograms were obtained. The presence of the mechanical obstruction was confirmed in all cases in which it was attempted. The procedure used to produce paralytic ileus caused diffuse fibrinopurulent peritonitis and moderate dilatation of the lower half of the small intestine. No dense adhesions were found which could cause a mechanical obstruction.

The results given in table 2 indicate that the average time required for the production of gas shadows on the roentgen film following mechanical ileus was three and one-half hours for a low and three hours for a high obstruction, and fluid levels were seen on an average of three and four hours later, respectively. The fact that fluid levels occurred at about the same time in both high and low obstruction was

31. Markowitz, J., and Campbell, W. R.: The Relief of Experimental Ileus by Spinal Anesthesia, *Am. J. Physiol.* **81**:101, 1929.

32. Steinberg, B., and Goldblaut, H.: Peritonitis, *Arch. Int. Med.* **42**:415 (Sept.) 1928.

at first puzzling. However, the fluid content was measured in several animals, and the amount necessary to form fluid levels was found to be very small, an observation that agrees with that of Wangensteen and Lynch. Additional explanation is given by Morton and Sullivan,<sup>29</sup> who show experimentally that a large amount of fluid is secreted in an isolated loop of the proximal small intestine, whereas in a similar loop in the distal portion of the small intestine a negligible amount is secreted.

The experiments in which paralytic ileus was produced did not show such consistent results. Gas was seen on the roentgen films on

TABLE 2.—*Experimental Data* \*

Dog	Type of Ileus	Point of Obstruction	Normal Abdominal Measurement, Cui.	Presence of Gas, Hrs.	Abdominal Measurement at Time of Appearance of Gas, Cm.	Presence of Fluid Levels, Hrs.	Abdominal Measurement at Time of Fluid Levels, Cm.
1	Mechanical.....	Lower ileum	46	4	46	6	47
2	Mechanical.....	Lower ileum	51	4½	51	8½	51.5
3	Mechanical.....	Lower ileum	52	4½	52	8½	54
4	Mechanical.....	Lower ileum	50	2	50	4	50
5	Mechanical.....	Lower ileum	53	2	53	4	53
6	Mechanical.....	Lower ileum	55	3	55	7	55.75
7	Paralytic.....	.....	47	6	48	6	48
8	Mechanical.....	Upper ileum	56	2	56	4	56
9	Mechanical.....	Upper ileum	48	2	48	8	48.5
10	Mechanical.....	Upper ileum	50	5	51	9	51
11	Paralytic.....	.....	55	5	55	48	59
12	Paralytic.....	.....	45	5	46	8	47.5
13	Paralytic.....	.....	45	5	47	7	47
					Gas	Fluid Levels	
Average number of hours after mechanical low obstruction.....					3½	6½	
Average number of hours after mechanical high obstruction.....					3	7	
Average number of hours after paralytic ileus.....					5¼	17¼	

\* Further studies now in progress on the roentgen signs in vascular occlusion of the bowel will be reported later.

an average of five and one-fourth hours and fluid levels seventeen and one-fourth hours after the operation. Disregarding experiment 11, a more consistent average was found. Since the exact time of the onset of the ileus is not known, its relation to the appearance of gas shadows is problematic.

#### TECHNIC

In cases in which acute obstruction of the bowel is suspected, it is generally conceded that the administration of the opaque meal, even in small amounts, is inadvisable and is unnecessary since the shadows cast by the gas-filled loops of bowel and the presence of fluid levels give sufficient roentgen evidence for diagnosis.

The earliest writers suggest the supine and erect positions and more recently the lateral and postero-anterior or anteroposterior recumbent positions have been introduced. The latter positions are used when the patient is too ill to sit erect.

Our routine in cases in which obstruction is suspected has been, when possible, to take projections in four positions: the supine, erect, and the anteroposterior or postero-anterior with the patient recumbent on his left and right sides. Occasionally, however, if the film made in the supine position obviously shows no distended bowel, the others are not taken.

The Potter-Bucky diaphragm is used when possible. In dealing with extremely ill patients, it is necessary to employ the bedside unit with a minimum of disturbance. A relatively high kilovoltage is necessary, with a milliamperage as high as

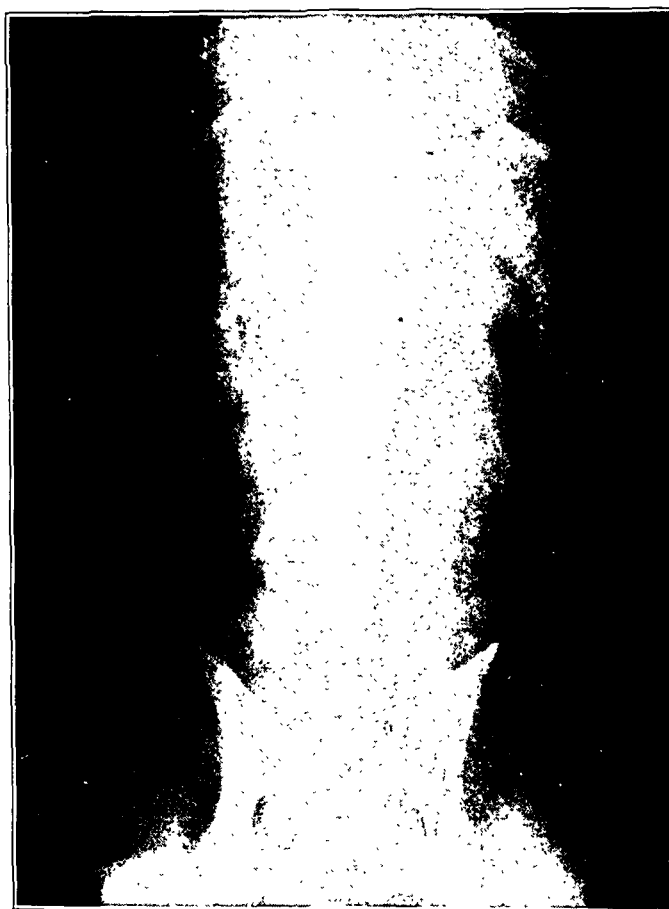


Fig. 1.—Roentgenogram of the abdomen (dog) made in the erect position four and one-half hours after low mechanical obstruction was produced; gas distended loops of the bowel are shown.

possible to allow for the shortest possible exposure as the patient is generally in pain and has difficulty in cooperating.

#### ROENTGEN DIAGNOSIS

Though the previous writers have emphasized the appearance of the "ladder effect" of the parallel loops of dilated intestine and the striated appearance of the mucosal folds (the so-called valvulae conniventes)

together with the fluid levels, few have called attention to the aid they give in determining the level of obstruction.

The character of the shadow of the distended intestine, its location on the film and the extent of the distended loops are the diagnostic criteria, which, when correlated with the history and physical findings, will determine the level of obstruction with a fair degree of accuracy in the majority of cases.

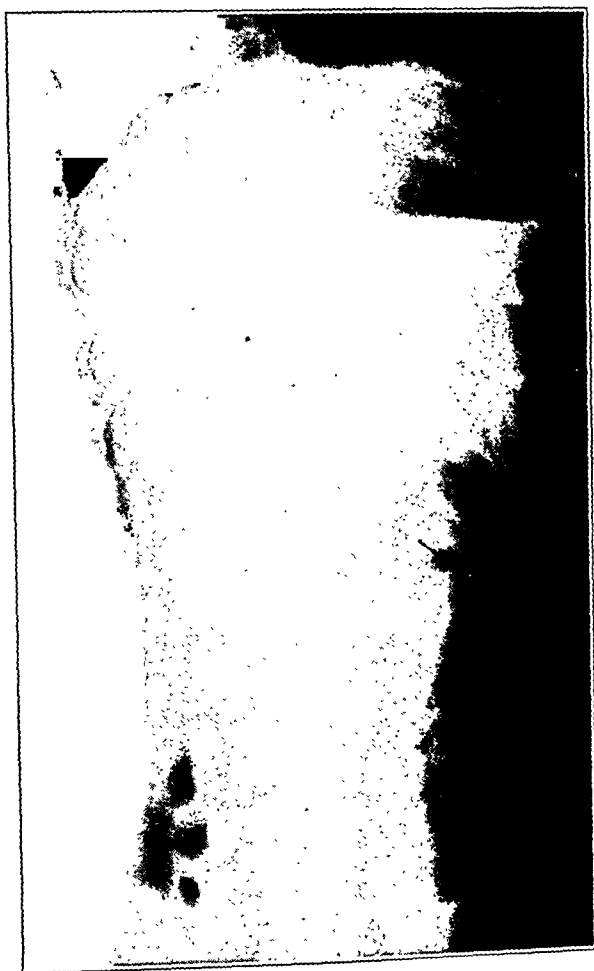


Fig. 2.—Same case as in figure 1 at eight and one-half hours. Fluid levels are present.

Realizing the importance of the characteristic shadows cast by the distended bowel, several fresh specimens of small intestine were studied after their removal within a few hours post mortem. They were distended with air and then roentgenograms made. One of these specimens is shown in figure 3, which includes the entire length of small intestine with the exception of the duodenum. It is interesting to note that the transition between the characteristic appearance of jejunum and ileum is fairly abrupt. The change is not so gradual that it cannot

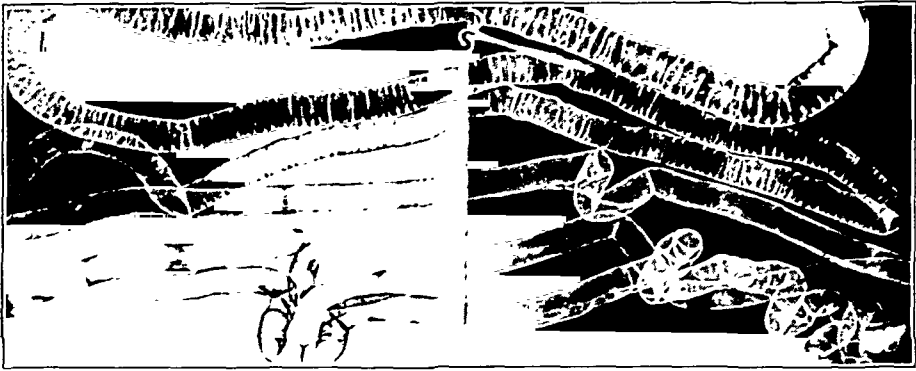


Fig. 3.—Fresh postmortem specimen of the entire small intestine (human), with the duodenum, distended with air. Note the rather abrupt change from the striated appearance of the jejunum to the smooth walled ileum.



Fig. 4.—Roentgenogram of the abdomen made twenty-four hours after operation, showing gas-filled loops of small intestine. No clinical distention was present.



be used as a point in determining the level of obstruction. The point of occlusion can usually be localized to one of four levels, namely: (1) jejunum, (2) upper portion of the ileum, (3) lower portion of the ileum and (4) large bowel.

The distended loops of small bowel are usually seen in the upper left quadrant, or at least in the upper two quadrants, when the obstruction is high, the shadows appearing progressively lower down and to

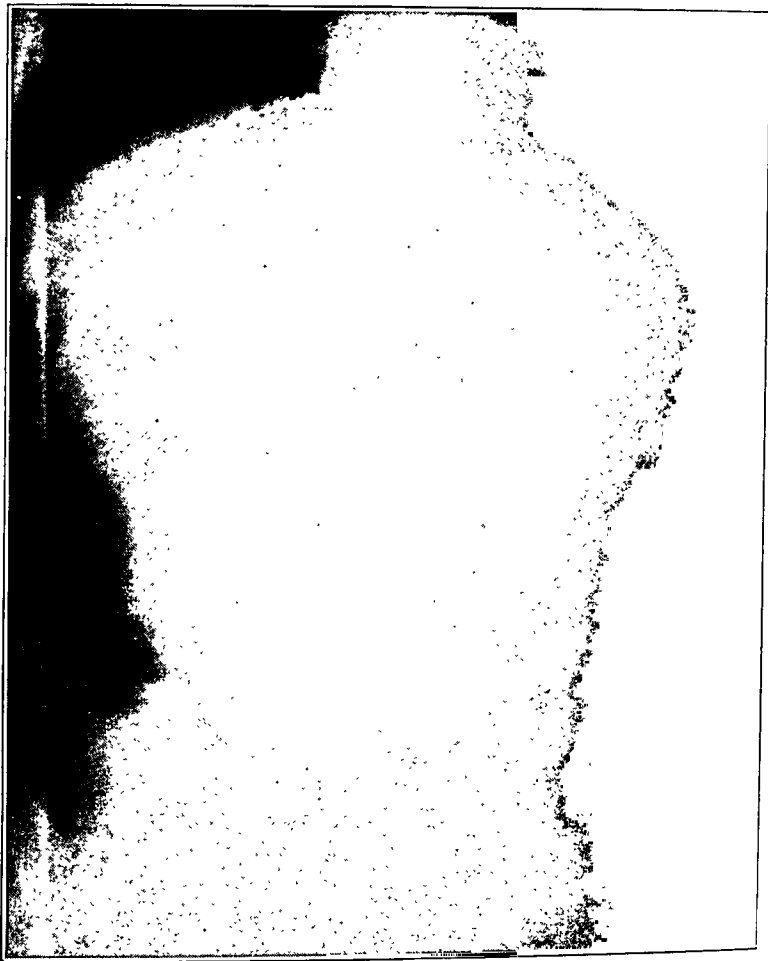


Fig. 5 (case 55).—Roentgenogram of the abdomen made in the erect position, showing typical fluid levels.

the right as the level lowers until the distention becomes general when a low obstruction exists. Further, with the point of occlusion in the large bowel, the added shadows of the dilated colon are seen proximal to the level and as a general rule at the periphery of the abdomen.

It might be well to point out here that, as figure 3 shows, one may see the smooth-walled ileum casting a sort of pseudostriated appearance when coiled on its mesentery. Striae or septums appear, but they do not run clear across the lumen and are not as close together as those of the jejunum, approaching more the appearance of the haustral markings

of the colon. A practical application of this is seen in figure 4 where the distended loops give this impression (postoperative film).

Using the foregoing diagnostic criteria, the cases of ileus seen at the Presbyterian Hospital within the last three years have been reviewed to determine first of all whether our roentgen findings were of aid, and second, to see whether the level was or could have been localized with any degree of accuracy from the roentgenographic evidence alone. Operative findings were correlated with the roentgen observations. The surgeon, in a few cases, could not localize the exact point of obstruction, a notation of "dilated loops of jejunum or ileum" being made only. Table 3 gives an analysis of the fifty-five cases of ileus seen during the past three years at the Presbyterian Hospital in which the roentgen



Fig. 6.—Same case as in figure 5 except that the patient was lying on the side.

examination was used as a means of diagnosis. It will be noted that there is a striking absence of clinical distention in the majority of cases, although the roentgenographic signs were definite. Forty-nine per cent showed absolutely no clinical signs of distention, while 23.6 per cent showed but a mild distention. Only 9 per cent showed a characteristic marked distention. Only 40 per cent showed the typical continuous projectile vomiting, the remainder showing but a variable degree. The most frequent site of obstruction was in the lower portion of the ileum (54.5 per cent). The next in frequency was the lower portion of the colon (18.1 per cent). The rest were high obstructions at variable locations (27.4 per cent).

It would seem from the foregoing analysis that, as Wangenstein and Lynch<sup>22</sup> pointed out, the clinical signs of obstruction with the exception of pain, as stated in textbooks, are really "ante mortem"

TABLE 3.—Analysis of Fifty-Five Cases of Ileus \*

Case	Age	Type of Ileus	X-Ray Readings		Operative Level	Fluid Levels	Duration of Symptoms	Clinical at Roentgen Examination	Vomiting	Results
			Preoperative Reading	Present Reading						
1	31	Mechanical	Lower ileum	Agreed	Middle ileum	Negative (supine)	23 hrs.	0	1	Recovered
2	47	Mechanical	Lower ileum	Agreed	Lower ileum	Negative (supine)	9 days (mild)	2	2	Recovered
3	21	Mechanical	Upper ileum	Agreed	Diff. sm. intestine	Positive	12 days (mild)	1	2	Recovered
4	34	Paralytic	Few loops ileum	Agreed	Few loops sm. intestine	Negative (supine)	2 days (mod.)	0	3	Recovered
5	30	Mechanical	Lower ileum	Agreed	Lower ileum	Positive	22 hrs.	2	2	Recovered
6	34	Mechanical	Sigmoid	Agreed	Sigmoid	Positive	5 days	2	3	Recovered
7	64	Paralytic	Diff. sm. intestine†	Agreed	Diff. sm. intestine	Negative (supine)	36 hrs.	1	1	Died
8	53	Mechanical	Lower colon	Agreed	Sigmoid	Negative	60 hrs.	0	3	Died
9	44	Mechanical	Middle ileum	Agreed	Middle ileum	Positive	16 hrs.	0	1	Died
10	29	Mechanical	Lower ileum	Agreed	Lower ileum	Positive	72 hrs.	3	3	Recovered
11	37	Mechanical	Middle ileum	Agreed	Lower ileum	Negative (supine)	18 hrs.	0	1	Died
12	73	Mechanical	Colon	Agreed, big intestine	Sigmoid	Negative	72 hrs. (mod.)	0	1	Recovered
13	56	Mechanical	Diff. sm. intestine	Agreed	Lower ileum	Negative (supine)	2 mos. (mild)	0	0	Recovered
14	4	Mechanical	Upper ileum	Agreed	Lower jejunum	Negative (supine)	12 hrs. (acute)	3	3	Recovered
15	17	Mechanical	Upper ileum	Agreed	Lower jejunum	Negative (supine)	96 hrs. (mild)	0	3	Recovered
16	41	Mechanical	Upper sm. intestine	Agreed	Lower ileum	Positive	20 hrs.	0	2	Died
17	60	Paralytic	Upper sm. intestine	Agreed	Diff. sm. intestine	Negative (supine)	24 hrs.	1	3	Died
18	49	Mechanical	Lower jejunum	Agreed	Lower ileum	Negative (supine)	18 hrs.	2	3	Recovered
19	45	Mechanical	Middle ileum	Agreed	Lower ileum	Positive	72 hrs. (mod.)	0	3	Died
20	24	Mechanical	Middle colon	Agreed	Middle colon	Negative (supine)	3 mos. (mild)	0	0	Died
21	59	Mechanical	No obstruction	Indeterminate	Slight diff. dist.	Negative (supine)	70 hrs. (mod.)	0	2	Recovered
22	42	Mechanical	No obstruction	Colon	Lower colon	Negative (supine)	96 hrs. (mod.)	2	2	Recovered
23	26	Paralytic	Indeterminate	Lower ileum	Diff. sm. intestine	Negative (supine)	24 hrs.	2	3	Died
24	40	Mechanical	Lower ileum	Agreed	Cecum	Positive	3 wks. (mild)	0	2	Died
25	35	Paralytic	Lower ileum	Agreed	Diff. sm. intestine	Positive	96 hrs. (mod.)	2	2	Died
26	31	Mechanical	Indeterminate	Lower ileum	Lower ileum	Negative (supine)	8 wks. (mod.)	2	2	Recovered
27	64	Mechanical	Lower colon	Agreed	Sigmoid	Negative	7 days (mild)	0	0	Died
28	51	Mechanical	Indeterminate	Lower ileum	Diff. sm. intestine	Negative (supine)	3 wks. (mild)	1	2	Died
29	28	Mechanical	Middle ileum	Agreed	Lower ileum	Positive	8 days (mild)	0	2	Recovered
30	2 mos.	Mechanical	Lower ileum	Agreed	Diff. sm. intestine	Negative (supine)	72 hrs.	1	1	Recovered
31	26	Paralytic	Indeterminate	Jejunum loops seen	No operation	Negative	(?)	3	1	Recovered
32	25	Mechanical	Indeterminate	Lower ileum	Diff. sm. intestine	Positive	14 hrs.	0	3	Recovered
33	36	Paralytic	Lower ileum	Agreed	Diff. sm. intestine	Positive	24 hrs.	2	3	Recovered
34	43	Mechanical	Indeterminate	Lower ileum	Jejunum, dist. seen	Negative (supine)	120 hrs.	2	3	Recovered
35	56	Mechanical	Indeterminate	Large intestine	Large intestine	Negative	4 mos. (mild)	2	(?)	Died
36	55	Mechanical	Lower ileum	Agreed	Lower ileum	Positive	3 wks. (mod.)	1	3	Recovered
37	59	Mechanical	Upper ileum	Agreed	Middle jejunum	Positive	36 hrs.	0	3	Died
38	65	Mechanical	Indeterminate	Agreed	Sigmoid	Negative (supine)	36 hrs.	1	3	Died
39	42	Mechanical	Lower colon	Agreed	Lower jejunum	Negative (supine)	(?)	0	1	Recovered
40	14	Mechanical	Upper ileum	Agreed	Middle ileum	Positive	20 hrs.	1	3	Recovered
41	27	Mechanical	Lower ileum	Agreed	Lower ileum	Positive	30 hrs.	0	3	Recovered
42	32	Mechanical	Lower ileum	Agreed	Lower ileum	Positive	8 hrs.	1	2	Recovered
43	43	Mechanical	Diff. sm. intestine	Agreed	Diff. sm. intestine	Positive	24 hrs.	1	3	Died
44	61	Paralytic	Diff. sm. intestine	Agreed	Diff. sm. intestine	Positive	3 days	3	3	Died
45	56	Mechanical	Indeterminate	Agreed	Middle ileum	Negative (supine)	48 hrs.	2	3	Recovered
46	3	Paralytic	Indeterminate	Diff. sm. intestine	Diff. sm. intestine	Negative (supine)	48 hrs.	1	3	Recovered
47	41	Mechanical (?)	Indeterminate	Diff. sm. intestine	Diff. sm. intestine	Negative (supine)	15 hrs.	1	1	Recovered
48	59	Mechanical (?)	No obstruction	No obstruction	No obstruction	Negative (supine)	11 days (mild)	0	2	Recovered
49	42	Mechanical (?)	Loop of jejunum	Agreed	No operation	Negative (supine)	2 yrs. (mild)	0	0	Recovered
50	27	Mechanical (?)	Few loops sm. intestine	Agreed	No operation	Negative (supine)	5 days (mild)	0	1	Recovered
51	51	Mechanical (?)	Indeterminate	Dist. loop of jejunum	No operation	Negative (supine)	10 days (mild)	0	1	Recovered
52	50	Mechanical (?)	Indeterminate	Dist. loop of jejunum	No operation	Negative (supine)	2 days	1	1	Recovered
53	13	Paralytic	Lower ileum	Agreed	No operation	Positive	4 hrs.	0	1	Recovered
54	17	Mechanical (?)	Dist. loop of jejunum	Agreed	No operation	Negative (supine)	8 hrs.	0	1	Recovered
55	54	Mechanical	Upper ileum	Agreed	Middle ileum	Positive				Recovered

\* Graded distention and extent of vomiting were marked as follows: 0, no distention; 1, mild distention; 2, moderate distention; 3, marked distention; 4, no vomit; 5, moderate vomiting; 6, moderate vomiting; 7, marked vomiting; 8, marked vomiting; 9, no vomit and no vomiting; 10, moderate vomiting; 11, moderate vomiting; 12, marked vomiting; 13, marked vomiting; 14, marked vomiting; 15, marked vomiting; 16, marked vomiting; 17, marked vomiting; 18, marked vomiting; 19, marked vomiting; 20, marked vomiting; 21, marked vomiting; 22, marked vomiting; 23, marked vomiting; 24, marked vomiting; 25, marked vomiting; 26, marked vomiting; 27, marked vomiting; 28, marked vomiting; 29, marked vomiting; 30, marked vomiting; 31, marked vomiting; 32, marked vomiting; 33, marked vomiting; 34, marked vomiting; 35, marked vomiting; 36, marked vomiting; 37, marked vomiting; 38, marked vomiting; 39, marked vomiting; 40, marked vomiting; 41, marked vomiting; 42, marked vomiting; 43, marked vomiting; 44, marked vomiting; 45, marked vomiting; 46, marked vomiting; 47, marked vomiting; 48, marked vomiting; 49, marked vomiting; 50, marked vomiting; 51, marked vomiting; 52, marked vomiting; 53, marked vomiting; 54, marked vomiting; 55, marked vomiting.

signs, coming on definitely only when the patient is in the majority of cases moribund. "Watchful waiting" in cases in which obstruction is suspected has, in the interval of observation, all too frequently lost valuable time during which the patient's resistance was gradually lowered, until, when the symptoms became definite, he was already to be considered a poor surgical risk. It is in this instance that the roentgen examination can be of aid in doubtful cases, and those slow to show clinical symptoms.

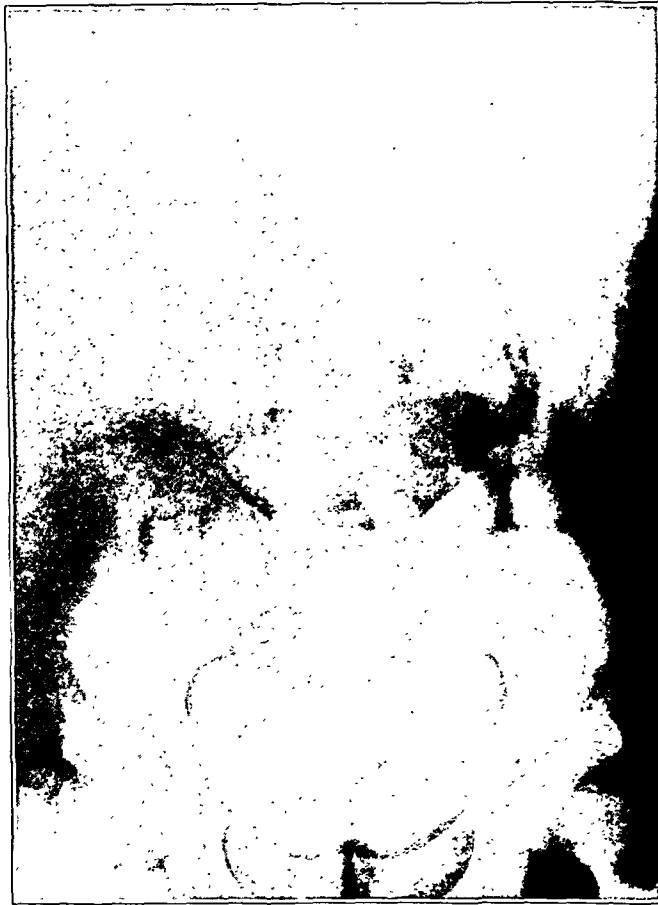


Fig. 7.—Barium filled dilated small intestine in a case of incomplete obstruction nine hours after barium was administered orally.

The films of the entire group of cases tabulated were reviewed without knowledge of the clinical findings except that the cases were those in which obstruction was suspected. On a close inspection of the films it was found that the level of obstruction could be located much more closely than the current report had ventured to state it, checking closely with the operative findings.

In order to facilitate an early diagnosis, every puzzling case of acute condition of the abdomen deserves at least a flat abdominal film

made with the patient in the supine position. Particularly is this true if the patient gives a history of a previous abdominal operation. One of the following case histories illustrates this point (case 55, figs. 5 and 6). The clinical findings were not definite since the patient had had some cramp-like pain but not of great severity, showed no distention and had vomited but twice; yet the abdominal films showed marked distention and fluid levels. Not only is the film of value in ruling out bowel obstruction, but other conditions may be ruled out by this procedure such as calcifying abdominal nodes or urinary calculi. If and when the flat film shows positive signs of distention, the other films can be taken as described elsewhere in the paper.

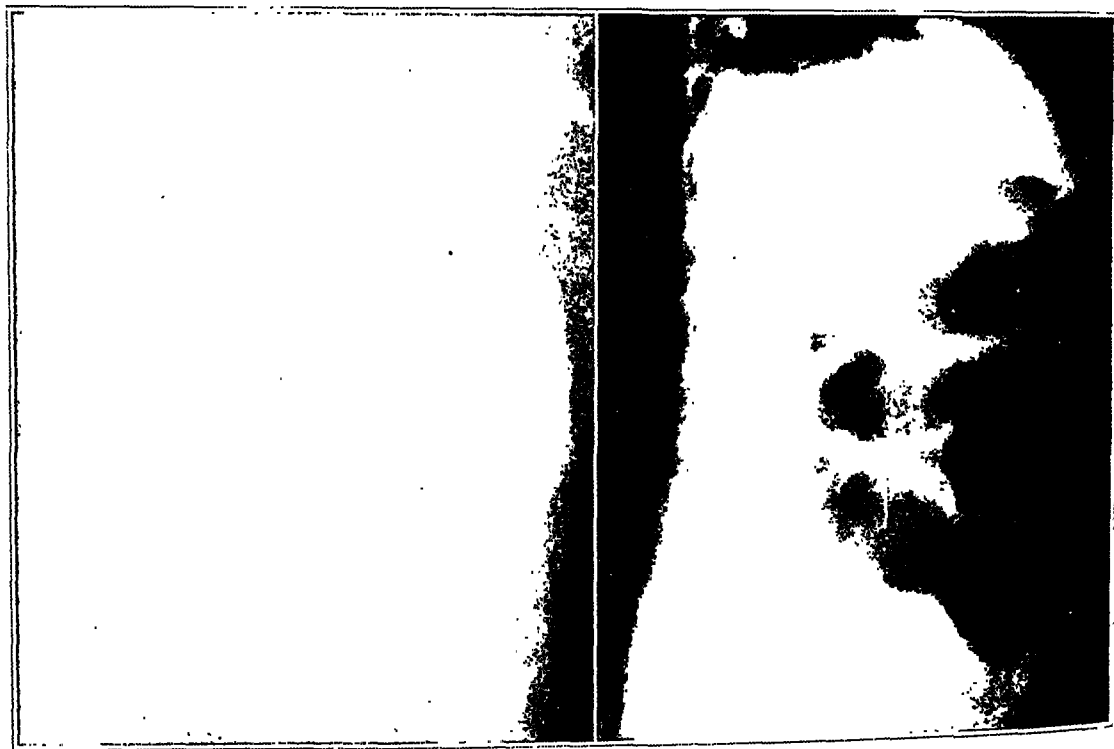


Fig. 8.—Roentgenograms of the abdomen made in the anteroposterior and lateral positions, showing typical "ladder" appearance and striated markings found in the upper portion of the small intestine, in a case of mechanical obstruction due to a postoperative adhesive band. The level of the obstruction was in the lower portion of the jejunum.

It has been pointed out by Case<sup>33</sup> that it is not unusual to find gas in variable amounts within the small intestine following abdominal operations. It was interesting to find it in such a large number of instances and to such a great degree in several cases picked at random from the surgical service at the Presbyterian Hospital. In ten such cases (table 4) there was a certain degree of distention in all except one.

33. Case (footnote 8, second reference).

in spite of the fact that none showed an alarming postoperative course. These results lead to the conclusion that postoperative ileus of surgical importance must be diagnosed with the utmost care. The condition noted on these films must be considered a definite paralytic ileus; however, not until subsequent films have demonstrated increasing distention and fluid levels does the picture become one of importance, and not until then should anything but conservative treatment be contemplated.

The differentiation between a purely mechanical and paralytic type of ileus is difficult when roentgen signs only are considered since they

TABLE 4.—*Analysis of Ten Cases*

Case	Operation	Extent of Manipulation of Intestine	No. of Hours Following Operation at Which X-Rays Were Taken	X-Ray Interpretation
55	Appendectomy	Very little	20	Many loops of mildly distended ileum
56	Splenectomy	None	24	Slightly distended lower ileum
57	Appendectomy	Very little	26	Moderately distended loops of ileum and jejunum
58	Appendectomy	Lower small intestine moderately manipulated	22	Moderately distended ileum and jejunum
59	Drainage of appendiceal abscess	Very little	20	Slightly distended lower ileum
60	Cholecystectomy	Very little (if any)	22	No distended loops of small intestine
61	Appendectomy	.....	18	Mildly distended loops of ileum and jejunum
62	Appendectomy	Lower ileum moderately manipulated	26	Mildly distended loops of ileum and jejunum
63	Appendectomy with drainage	Very little	28	Mildly distended loops of ileum and jejunum
64	Repair of ventral hernia	Intestine moderately manipulated	28	Mildly distended loops of ileum and jejunum

both give the same picture on the roentgen film in the majority of cases. However, one suggestive sign is sometimes available when the paralytic ileus follows peritonitis. In this case the walls between the dilated loops are sometimes seen to be thickened due to the exudate over the surface of the intestine.

Mention has been made of the hazard of using a barium sulphate suspension by mouth as a contrast medium in acute cases. However, its recognized value in partial obstructions in the small bowel of long standing is not to be deprecated. Cases of this type are often picked up in the routine gastro-intestinal examination. Such a case is shown in figure 7 where there is a moderate degree of dilatation and disturbance of motility of the bowel due to a partial obstruction following a

malignant condition of the large bowel, the film being taken nine hours after the administration of the barium sulphate meal. This type of case does not show fluid levels in the small bowel unless the obstruction becomes complete. This was the exact course of events in this case (24).

A barium sulphate enema may be used in certain cases in which the differentiation of a dilated small intestinal loop from that of the shadow of the large bowel is difficult. Barium outlining the colon will serve to

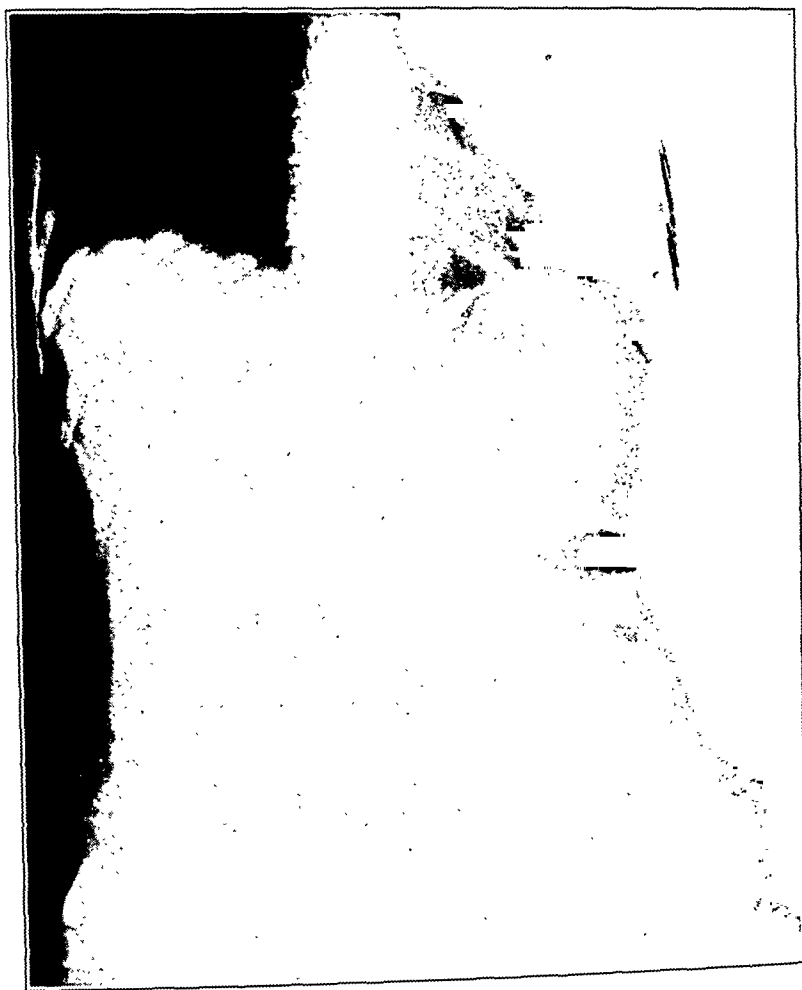


Fig. 9.—Roentgenogram of the abdomen made in the erect position, showing typical fluid levels.

prove that the distention involves the small or the large intestine only as the case may be.

#### REPORT OF CASES

CASE 40 (figs. 12 and 13).—A girl, aged 14, came to the Vanderbilt Clinic complaining of abdominal pain of fifty hours' duration. At the onset she noticed a dull, aching, midabdominal pain which later increased in severity and localized in the right lower quadrant. She became nauseated and vomited two or three times during the day. The pain was more generally distributed on the second day, although it was greatest in the right lower quadrant. Physical examination

disclosed an extremely tender and rigid abdomen. A diagnosis of acute appendicitis with diffuse peritonitis was made. At operation the diagnosis was confirmed; the appendix was removed and the abdomen drained. The postoperative convalescence was slow, and on the nineteenth day the abdomen became quite distended,

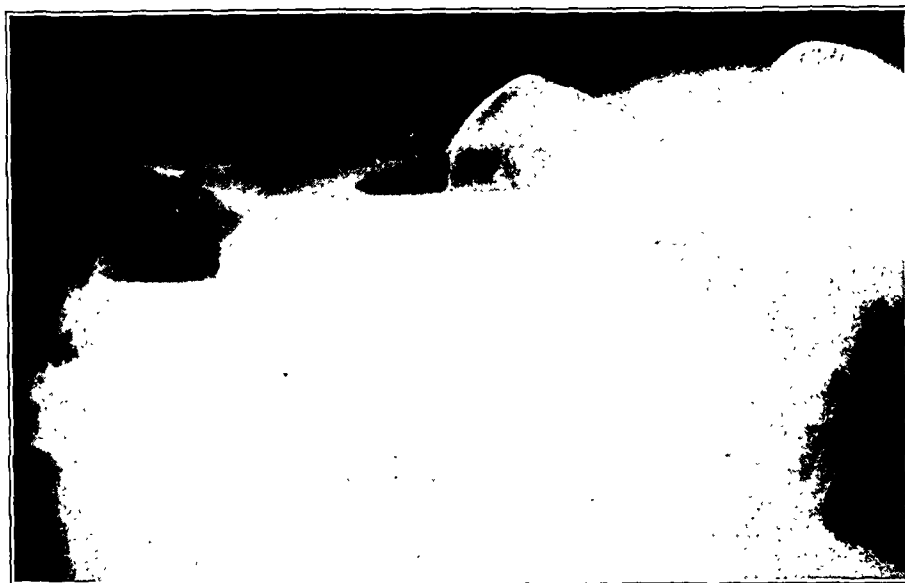


Fig. 10.—Same case as in figure 9, with the patient lying on the right side.

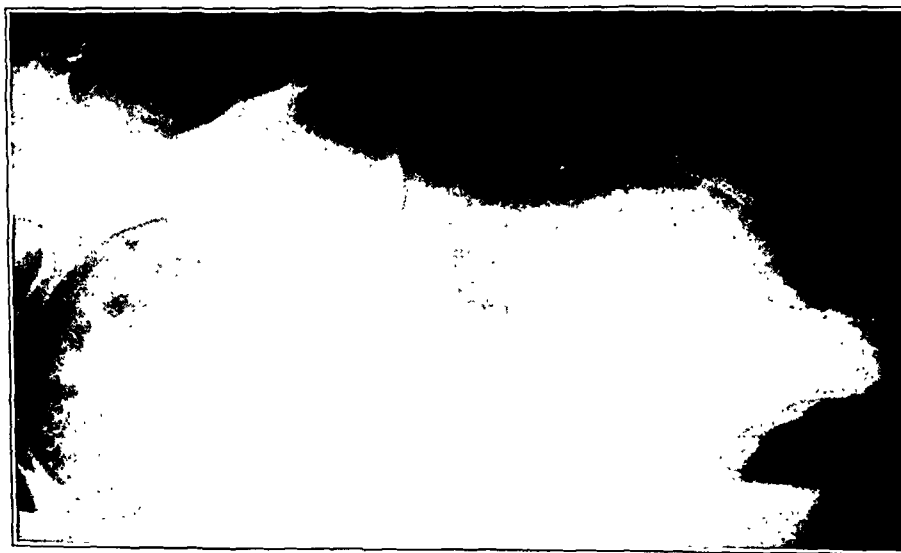


Fig. 11.—Same case as in figures 9 and 10, with the patient lying on the left side.

and the patient had colicky pain and vomited many times. The roentgen films at this time disclosed markedly dilated loops of small intestine containing gas and fluid levels. A jejunostomy was performed, the adhesions were freed and the patient did well thereafter, being discharged on the thirty-fourth day.



This case represents a mechanical ileus caused by adhesions developing relatively soon following appendectomy with drainage. The roentgen findings were quite characteristic within twenty-four hours following the onset.

CASE 44 (fig. 14).—A man, aged 61, entered Vanderbilt Clinic complaining of abdominal pain, distention and vomiting of three days' duration. At the onset he noticed moderate pain in the lower portion of the abdomen which became more severe during the day, gradually localizing in the right side. He vomited several

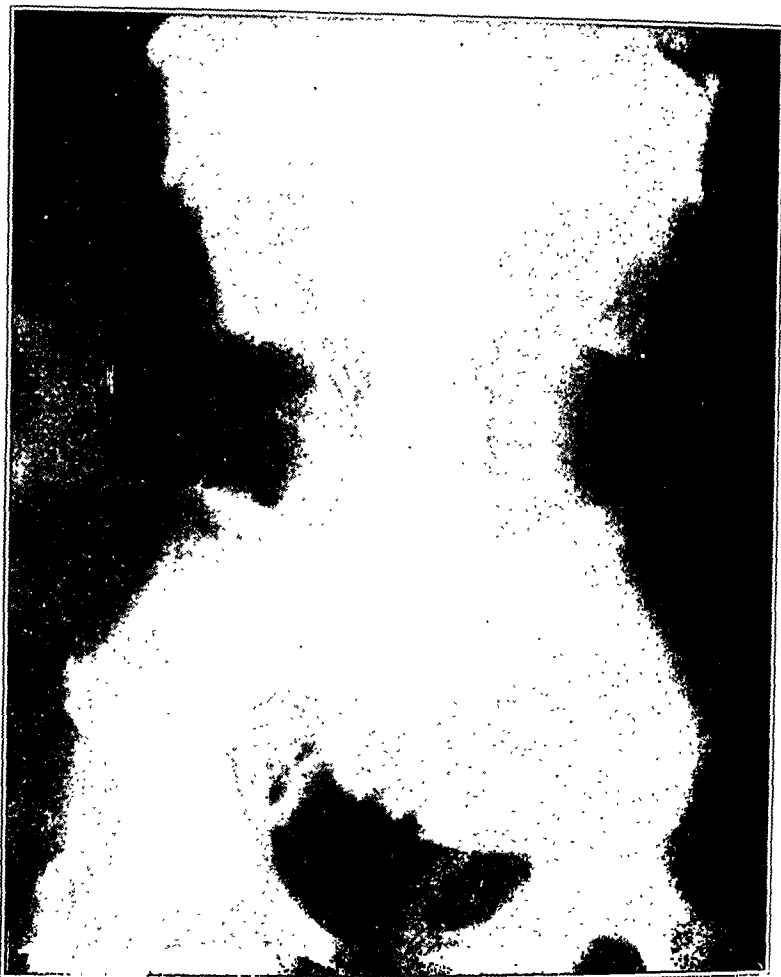


Fig. 12 (case 40).—Roentgenogram of the abdomen made in the supine position, showing typical shadows of distended small intestine.

times. The pain did not increase in severity during the second day, but he vomited much more frequently and a slight degree of abdominal distention was noticeable. On admission the pain was severe and diffuse; the patient vomited continuously and the abdominal distention was marked. Physical examination disclosed a full and tense abdomen with diffuse tenderness and rigidity, most marked in the right lower quadrant. The roentgenograms made in the supine and erect positions with the patient lying on his side presented evidence of markedly distended small intestine. The distended loops were most prominent in the left upper and right lower quadrants, and numerous fluid levels were present. At operation an acutely inflamed perforated appendix, generalized peritonitis and marked distention of the small

intestine were found. The patient died following the development of a postoperative pneumonia.

This case represents a paralytic (adynamic) ileus following diffuse peritonitis, in which numerous fluid levels as well as gas-distended intestinal loops were observed on the roentgenograms.

CASE 55 (figs. 5 and 6).—A man, aged 21, entered Vanderbilt Clinic complaining of severe, intermittent pain in the lower portion of the abdomen of six hours' duration, most marked in the left side. He had had an appendectomy with drainage five years previously. Four hours previous to the onset of the present attack he had eaten a large meal of corn muffins and hamburger sandwiches. He was nauseated and had vomited twice previous to his admission. Physical examination revealed a rigid and extremely tender abdomen, which did not move with respiration. The roentgenograms presented evidence of numerous distended loops of

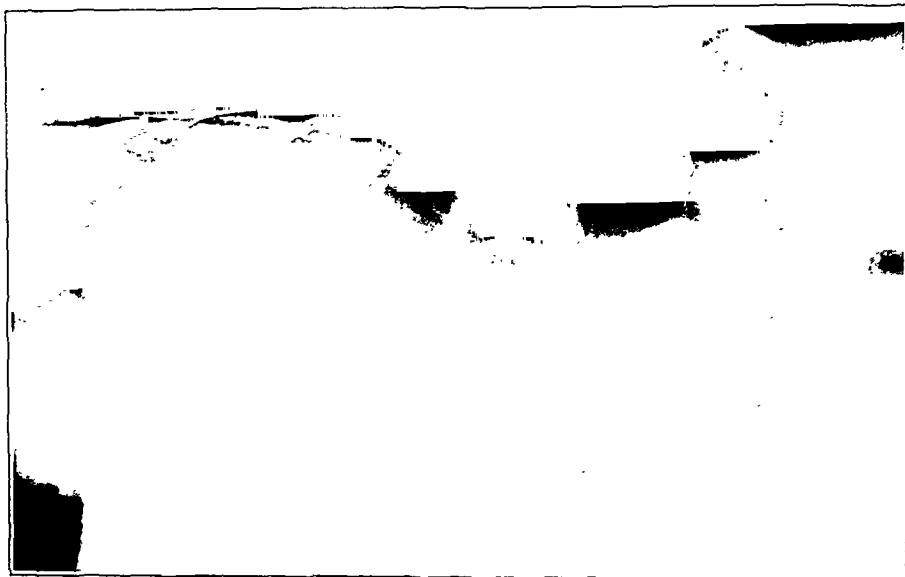


Fig. 13.—Same case as in figure 12, with the patient lying on the right side. Note the distended small intestine.

jejunum, a few distended loops of ileum and multiple fluid levels. At operation the small intestine was seen to be obstructed in the first part of the ileum by a tough, fibrous band originating at the old operative scar. The intestine was markedly distended proximal to and collapsed distal to the obstruction. The patient had a stormy postoperative course with bronchopneumonia, but ultimately recovered and was discharged on the forty-ninth day.

This case represents the earliest diagnosis in the series of mechanically obstructed cases. The symptoms were indefinite; the patient had vomited only twice previous to admission, and no abdominal distention was present. The decision to operate was based to a great extent on the information obtained from the roentgenograms.

CASE 4 (fig. 15).—A woman, aged 34, entered Vanderbilt Clinic complaining of pain in the lower portion of the abdomen of two days' duration. She had had

three attacks of moderately severe abdominal pain lasting from one to four days during the previous five months. At the onset the pain was severe and steady, located in the lower portion of the abdomen, more marked on the left side but

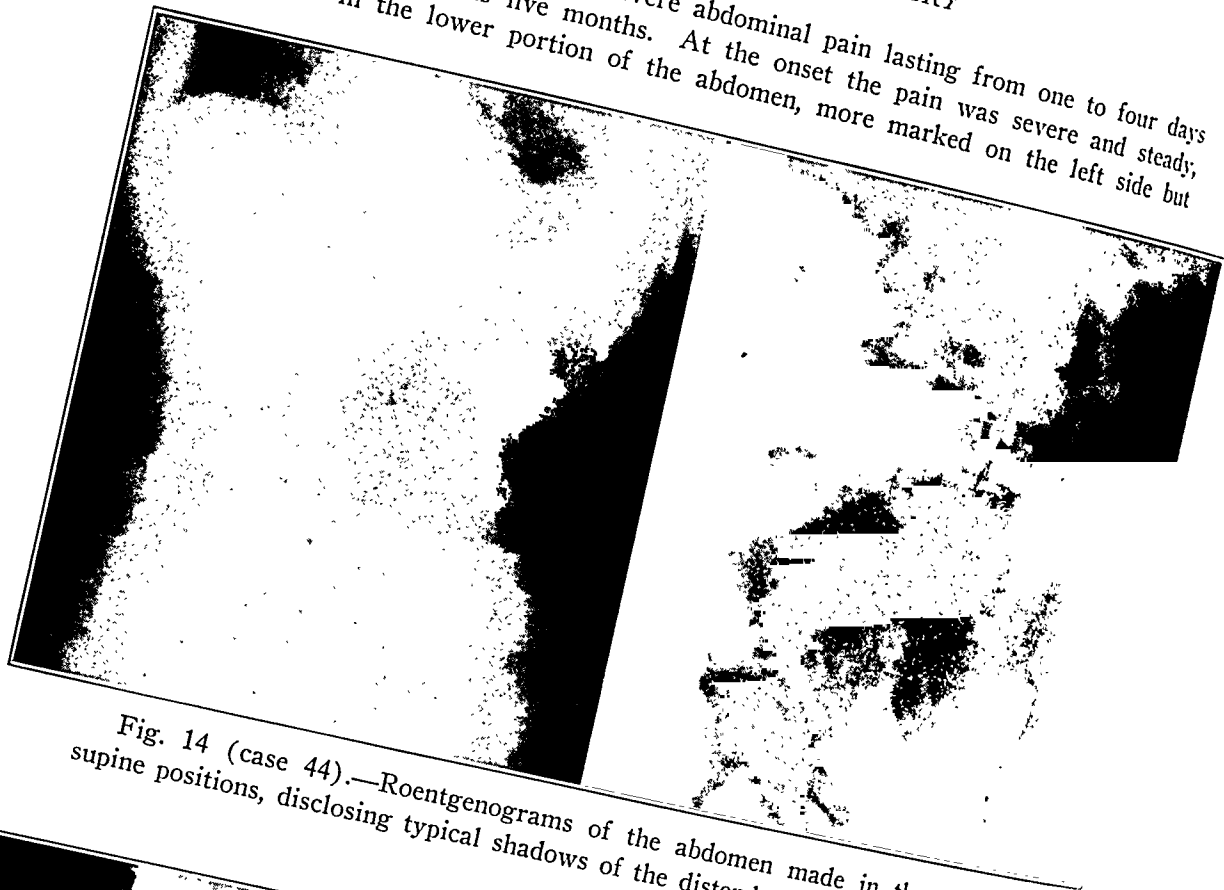


Fig. 14 (case 44).—Roentgenograms of the abdomen made in the erect and supine positions, disclosing typical shadows of the distended bowel and fluid levels.

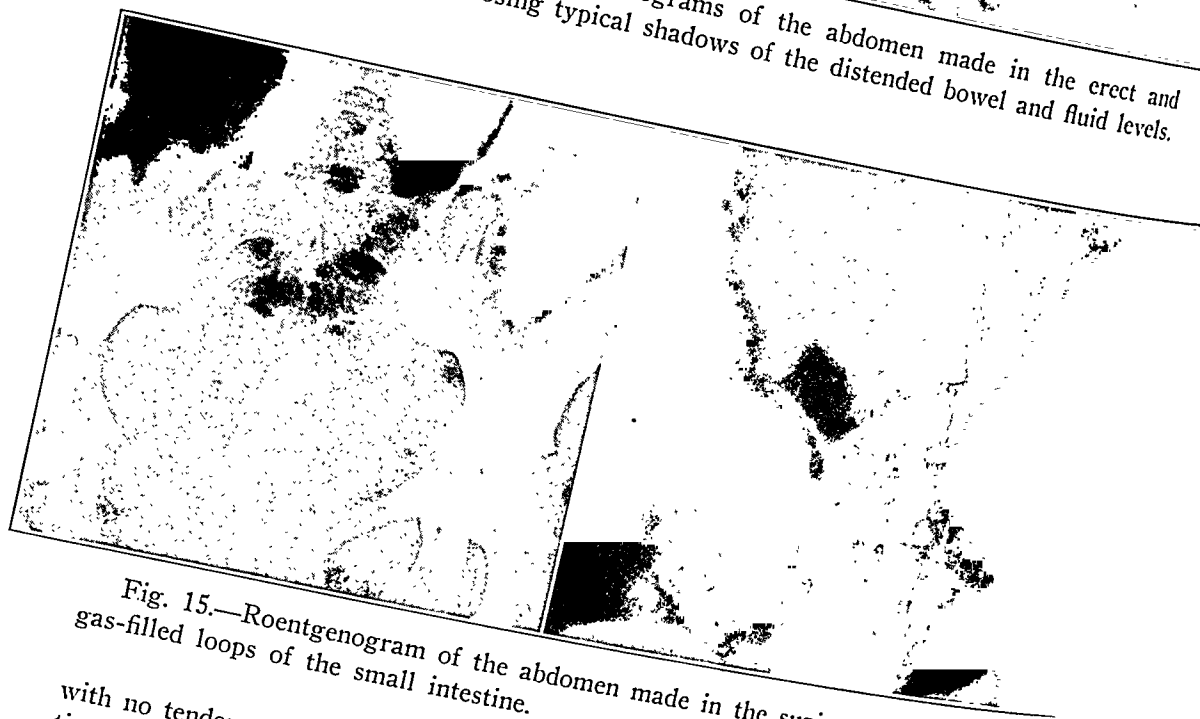


Fig. 15.—Roentgenogram of the abdomen made in the supine position, showing gas-filled loops of the small intestine.

with no tendency to radiate to the groin. She was nauseated and vomited several times. During the second day the pain became intermittent with its greatest intensity in the left lumbar region, the epigastrium and the right lower quadrant. She frequently passed small quantities of urine, associated with severe suprapubic pain.

The menses started on the second day, although the previous attacks had not been associated with menstruation. Physical examination disclosed moderate diffuse tenderness with its greatest intensity in the right lower quadrant and no involuntary rigidity. Roentgen films in the supine position showed evidence of two or three distended loops of small intestine which were thought to be the lower portion of the jejunum or the upper portion of the ileum. At operation a greatly distended colon and alternately contracted and distended segments of small intestine were found. A twisted ovarian cyst which showed signs of early necrosis was found in the pelvis and was resected. The postoperative course was uneventful.



Fig. 16 (case 18).—Roentgenogram of the abdomen made in the supine position, showing but three or four loops of distended small intestine. A very early manifestation of acute mechanical ileus, proved at operation.

This is a case of reflex paralytic ileus caused by a twisted ovarian cyst in which no evidence of peritonitis was observed at operation. The roentgenograms presented evidence of gas-distended loops of small intestine.

CASE 18 (fig. 16).—A woman, aged 49, entered Vanderbilt Clinic complaining of severe abdominal pain of eighteen hours' duration. She had had an appendectomy, excision of calcified mesenteric lymph nodes and liberation of omental adhesions without drainage six months previously. She felt very well following the

operation until about ten days previous to admission, at which time she had an attack of pain in the lower portion of the abdomen, severe and cramplike, associated with nausea and vomiting. The pain subsided in approximately twelve hours, following which she felt quite well again. The present attack was characterized by severe intermittent, nonradiating abdominal pain, more intense below and to the left of the umbilicus. During the second day, although the pain was of the same character, it had increased in severity, and the patient vomited frequently. No suggestive urinary symptoms were present. Physical examination revealed an acutely ill patient with a slight fulness below the umbilicus, a mild rigidity of the left rectus muscle and a moderate diffuse abdominal tenderness, greatest in the left lower quadrant. The roentgen films of the abdomen in the supine position disclosed some gas-filled coils of jejunum in the midabdominal region. The level of obstruction, therefore, was thought to be near the jejuno-ileal junction. At operation the bowel was greatly dilated proximal to and contracted distal to a dense adhesive band which obstructed it in approximately the first foot or two of the ileum. The post-operative convalescence was uneventful, and the patient was discharged on the eighteenth day.

This was a relatively early case of mechanical obstruction caused by an adhesive band following an appendectomy without drainage six months previously, in which the roentgen-ray findings were definitely positive.

#### SUMMARY

Gaseous distention of the bowel which can be detected roentgenographically was found, experimentally in dogs, to be present on an average of three and one-half hours following acute high mechanical obstruction.

In low obstruction it was found to occur in approximately the same length of time, namely, three hours.

Fluid levels were demonstrable, even though the intestine contained a small amount of fluid, in approximately from three to four hours after the appearance of gas.

The time interval between the appearance of gas and fluid levels was found to be about the same in both high and low mechanical obstruction.

Gas and fluid levels were produced in experimental paralytic ileus, the latter appearing at about the same interval following the recognition of gas as in the cases of mechanical obstruction.

Roentgen findings are evident before clinical findings are definite.

A new diagnostic point has been presented, namely, the relatively abrupt disappearance of the striae in the shadow of the distended jejunum as it approaches its junction with the ileum. This makes it possible to determine the level of obstruction much more closely than heretofore has been considered possible.

The majority of abdomens after operation will show a certain degree of ileus, even though the clinical findings are not alarming.

A barium sulphate meal is inadvisable if acute intestinal obstruction is suspected and is unnecessary for the diagnosis of this condition.

# INJURIES OF THE THORAX

## SERIOUS PLEUROPULMONARY COMPLICATIONS FOLLOWING A FREE INTERVAL

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That in injuries of the head serious complications frequently appear following a free interval is generally known. I have not been able to find any references to this sequence in injuries of the thorax, and for that reason feel that it is advisable to report five instances that have come under my observation during the past eighteen months.

In all, the injury was a simple blow on the thorax. In two there was a fracture of one rib, and in three no injury to the thoracic cage was demonstrated. In only one was the injury deemed important at the time it occurred, and in this case the patient was kept in bed because of repeated slight hemoptysis. In the two in which a rib was fractured, this was not discovered until after the onset of the late complication.

In three cases, spontaneous pneumothorax with infection of the pleural cavity occurred at intervals of one, four and five weeks, respectively, after the injury. In the fourth case, simple empyema developed two weeks after the injury. In the fifth case, the symptoms of intrapleural hemorrhage appeared six weeks after what had seemed to be a negligible injury.

### REPORT OF CASES

CASE 1 (Augustana Hospital).—*Blow on the thorax; hemoptysis; spontaneous pyopneumothorax one week later.*

J. K., a messenger boy, 17 years old, while running across lots through the snow, tripped over a low wire fence and fell, striking the left side of the thorax on the ground. The wind was knocked out of him, and as he got up he coughed up some blood. Being an employee of the hospital, he walked into the building, where he was cared for by an intern, who strapped the left side of the chest and, because of the hemoptysis, put him to bed. The next morning he was seen by Dr. Anders Frick, who found no abnormal physical signs. A roentgenogram taken that day was similarly negative. Slight hemoptyses continued for several days, but these stopped, and at the end of a week the patient was told that he could go home the next day. That night while sitting up in bed, he had a sudden severe pain in the right side of the thorax; he became dyspneic, coughed severely and from that moment was desperately ill. Physical and roentgen examinations showed hydro-pneumothorax on the right side. Aspiration gave a blood-tinged serous fluid containing streptococci. The patient was treated first by aspiration, later by closed drainage and finally by rib resection. A roentgenogram taken after the removal

of the fluid showed an atelectasis of the right lower lobe. This cleared up as the lung reexpanded. The patient improved gradually under treatment and eventually made a complete recovery.

CASE 2 (Columbus Hospital).—*Blow on the thorax with fracture of rib; development of spontaneous pyopneumothorax five weeks after the injury; infection of the fractured rib.*

Mr. J. W., a structural steel worker, 52 years old, fell several stories, lighting on some girders. He was considerably bruised, but the only apparent serious injury was a fracture of both bones of the lower portion of the right leg. Five weeks afterward, during which time he was in the hospital and had neither fever nor thoracic symptoms, he suddenly developed a severe pain in the lower right side of the thorax. A roentgenogram taken the next day, at which time the temperature was 102 F., showed fluid in the right lower pleural cavity. The patient was in a recumbent position when the film was exposed and air, if it was present, was not demonstrated. The day after the onset of pain, he began raising increasing amounts of foul purulent sputum and continued raising as much as 23 ounces a day until I first saw him. Roentgenograms taken in the interim showed pyopneumothorax with multiple fluid levels. Aspiration gave foul smelling pus similar to that which the patient was raising. This contained among mixed organisms many fusiform bacilli and spirochetes. Following rib resection, the cough stopped immediately and the patient's condition rapidly improved. He continued to have a slight fever, and after several weeks an area of deep fluctuation appeared in the soft tissues of his lower right side of the thorax. Exploration of this area led to the eighth rib in the midaxillary line. The rib, which was the focus of an abscess containing about 100 cc. of pus, was broken sharply across, and the ends of the ununited fragments were extensively infected. The infected rib was resected, and the wound was packed. Following this operation, the patient became afebrile and eventually made a complete recovery.

CASE 3 (Cook County Hospital).—*Blow on the thorax; development of spontaneous pyopneumothorax three and a half weeks after the injury.*

Mr. A. M., a machinist, 32 years old, fell from a chair, striking the lower right side of the thorax on a window ledge and his forehead on the floor. A laceration at this latter site seemed the most serious injury. His chest was sore for three or four days but not sufficiently so to keep from his work. About two weeks later he again noticed slight pain and soreness in this location in his thorax. This continued for about a week, and then one morning as he was getting out of bed, a sudden severe pain developed in that area, so severe that the patient lay back on the bed and was unable to rise. From that moment he was acutely ill. He entered the Cook County Hospital the next day. His temperature was 102 F., pulse rate 110 and respiration 30. Physical examination showed signs of fluid at the base of the right lung, and this was verified by the roentgenogram. His fever varied between 101 and 104 F. and was septic in type. For three weeks after his entrance to the hospital his cough was nonproductive, but then it gradually increased in severity and he began raising large amounts of foul purulent sputum. I first saw him three days after this. Physical examination gave the signs of fluid and air in the right pleural cavity. Aspiration below the angle of the scapula gave foul smelling air. Rib resection performed the same day showed an extensive pyopneumothorax. The pus was thin, brownish and foul, and contained fusiform bacilli and spirochetes. The cough stopped immediately after the operation, and one week later, at the time this was written, the patient was convalescing satisfactorily.

CASE 4 (Augustana Hospital).—*Injury to the thorax; fracture of one rib; development of empyema two weeks after the injury.*

Mr. M. A., a laborer, 38 years old, received an injury to the lower right side of the thorax while wrestling. The pain was severe enough so that the same day he consulted a physician who strapped his side. He continued up and about and felt well save for the pain in his side. Two weeks later, fever, weakness and sweats developed. The patient was seen by his family physician, who made a diagnosis of empyema of the right pleural cavity. He was sent to the hospital where the diagnosis was verified by the roentgenogram. The empyema was drained without resection of a rib, and he made an uneventful convalescence save that a draining sinus persisted. Roentgenograms taken several months later showed that the empyema cavity was obliterated, but that there was osteomyelitis of the right fourth rib in the midclavicular line at the site of an old fracture.

CASE 5 (Springbrook Sanatorium).—*Blow on the thorax; development of symptoms of severe hemothorax six weeks later.*

D. B., a youth, 18 years old, suffered a severe blow on the lower right side of the thorax in an automobile accident in August, 1930. The wind was knocked out of him for a few minutes, but shortly he was all right and able to continue his activities. He continued his work and had no complaint until some time in October, when he developed a cough and began to feel bad. He went to bed for a few days, but then got up and continued his work. At this time he was running a slight fever, but he disregarded it and continued up and about until the last part of November, when he consulted a physician, who made a diagnosis of pleural effusion. His chest was tapped, and a few cubic centimeters of bloody fluid was obtained. About the first of December he entered the Springbrook Sanatorium. Physical examination showed signs of fluid in the right pleural cavity, and his heart was displaced far to the left. His fever was high, and pulse and respirations rapid. Attempts to aspirate gave only a few cubic centimeters of bloody fluid. Operation for evacuation of clotted blood was advised and refused. The patient failed gradually, and died on Jan. 24, 1931. At autopsy, the right pleural cavity was found practically filled with a large firm mass which at first sight appeared to be a tumor. It was only when it had been removed and cut open that it was recognized as a mass of partially organized blood clots. Search for a fractured rib failed to show one.

#### COMMENT

In the first three cases the sudden onset of intense pain and the almost immediate appearance of severe pyopneumothorax suggests strongly that a focus of infection in the lung ruptured into the pleural cavity. In each case the symptoms and signs of severe sepsis ensued within twelve hours. The fact that in two of them the infecting organisms were fusiform bacilli and spirochetes further suggests that the infection came from the air passages to which these organisms, normal inhabitants of the mouth and pharynx, have ready access. It is well known also that in man the finer air passages normally harbor bacteria.

These facts make it seem probable that in these cases the blow caused a contusion or laceration of the lung. It is well known that this can occur with or without fracture of the ribs and that such an area of injured lung is frequently the site of a lobular pneumonia, the local



necrosis and hemorrhage producing favorable conditions for the growth of the bacteria normally present. If the area of injured lung were small and the infection limited to it, one can readily understand how it would not produce symptoms until necrosis or dissolution of the clot had permitted a rupture into the free pleural cavity.

In the two cases in which there was osteomyelitis of a fractured rib, it is probable that infection here was secondary to that of the pleural cavity. Hematogenous infection in a fracture is extremely rare, and especially so with the organisms found in these cases.

In the first case there is another possible explanation. In this there was a massive atelectasis of the lower lobe on the affected side. This was caused either by aspiration of gum which the patient had in his mouth at the time he fell or simply by the blow on his thorax. Bradford called attention to the high incidence of atelectasis secondary to blows on the thorax among the wounded in the World War. Whatever the cause of the atelectasis, it is conceivable that the atelectasis caused the rupture of the lung. As the atelectatic lung contracts, that adjacent to it expands. Raynaud found that in dogs this force of expansion was frequently sufficient to rupture the lung. I know of no instance in which this has been reported as occurring in man, but have seen recently a case of foreign body atelectasis complicated first by pneumothorax and later by pyopneumothorax. In this case, as in most cases of nontuberculous pyopneumothorax, the infecting organisms were fusiform bacilli and spirochetes.

In the fourth case there was no communication between the empyema cavity and the lung. This was probably an instance of late infection of a pleural hematoma or an instance in which the lung infection extended to the pleural cavity, as in ordinary pneumonias, without necrosis and rupture of the lung. Whether or not the latter occur must certainly depend on the nature and extent of the lung injury and on the type of infecting organisms. Fusiform bacilli and spirochetes favor necrosis.

In the fifth case it is difficult to say what precisely was the sequence of events. The bleeding may have immediately followed the injury and failed to give severe symptoms until the clot formed and infection developed. It is conceivable that a vessel was injured but not broken at the time of injury and that rupture of an aneurysm occurred weeks later. Bleeding started at the time of injury may have been slow and recurrent.

#### SUMMARY

Five cases are reported in which a free interval intervened between a blow on the thorax and the development of serious pleural or pleuropulmonary complications. In three instances the complication was spontaneous pyopneumothorax, in one simple empyema and in one profuse hemorrhage into the pleural cavity.

# FORTY-EIGHTH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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## CONGENITAL DEFORMITIES

*Congenital Torticollis.*—Bargellini<sup>1</sup> presented reports of three cases of congenital torticollis in which operation was performed when the patients were 35 days, 1½ months and 4 months of age, respectively. Two of the infants were delivered by podalic version and the third by an anomalous presentation, not specified. Abnormal inclination of the head and a tumor in the sternal head of the sternocleidomastoid muscle were noted by the mothers. At the time of operation definite facial asymmetry was seen by the author. A globular dusky mass was removed from the sternal head of the muscle, and both the sternal and clavicular attachments were severed; likewise the platysma and the deep cervical fascia. No anesthesia was used. Microscopic sections of specimens showed similar changes: intramuscular fibrosis, atypical growth in size and direction of muscular fasciculi and no evidence of hemorrhage. Postoperative therapy consisted of the weekly reapplication of a collar (type not specified) for two months. Complete recoveries with disappearance of facial asymmetry were reported. The author concluded

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This Report of Progress is based on a review of 217 articles selected from 326 articles appearing in medical literature approximately between Dec. 5, 1931, and April 2, 1932. Only articles which seemed to represent progress were selected for abstracting.

1. Bargellini, D.: *Chir. d. org. di movimento* **16**:415 (Oct.) 1931.

that the lesions were hereditary or intra-uterine in origin since lesions were found in infants delivered by cesarean section; extensive facial asymmetry was noted on early postnatal examination; there was absence of hemorrhage in the specimens, and a fairly long-existing cicatrix formation was observed. The reasons in favor of early operative intervention were: There was absence of danger; the deformity was corrected; preventive intervention was nearly always ineffective; increase in craniofacial asymmetry and scoliosis were prevented, and prolonged therapy was not required.

[ED. NOTE.—While there are many arguments in favor of the prenatal presence of muscular torticollis in cases with fibromas, there are also numerous instances in which difficult and rather violent deliveries have been accompanied by definite hematomas of the sternocleidomastoid muscles. Overlying cutaneous ecchymoses have been noted.]

*Congenital Dislocation of the Hip.*—Galland<sup>2</sup> stressed numerous points in the postreduction care of congenital dislocation of the hip, which he considered essential if good results were to be obtained. The whole article should be read as it could not be readily summarized. It gave an excellent review of postoperative treatment.

*Anomalies of the Tarsal Scaphoid.*—Schröder<sup>3</sup> reported the finding of an os supranaviculare pedis, an accessory bone between the superior edge of the scaphoid and the astragalus. Its origin was apparently explained by the fact that normally the scaphoid arose from two nuclei, one dorsal and the other plantar, which fused early. Failure to complete fusion might leave an accessory bone, to the presence of which pain might ultimately direct attention. The author found no evidence that these accessory bones were the remains of Köhler's disease. The one histologic examination (performed by Müller) recorded in the literature was negative. Anomalies of the tarsal scaphoid bone were rare.

[ED. NOTE.—Attention should be called to the importance of tarsal anomalies in compensation litigation. A case of the foregoing syndrome was recently seen in a toe-dancer by one of the authors. The question of a fracture, a calcific deposit or a congenital anomaly was raised. A roentgenogram of the other foot might help.]

*Spina Bifida Occulta.*—A case of spina bifida occulta of the fifth lumbar vertebra with symptoms of gradually increasing pain in the lower part of the back for two years was reported by Estor and Estor.<sup>4</sup> Conservative measures failed to give relief and the fifth lumbar vertebra was exposed by operation. An absence of the spinous process and a failure of the laminae to fuse were found. This confirmed previous

2. Galland, W. I.: Surg., Gynec. & Obst. **54**:88 (Jan.) 1932.

3. Schröder, F.: Deutsche Ztschr. f. Chir. **233**:306, 1931.

4. Estor, E., and Estor, D.: Rev. d'orthop. **18**:664 (Nov.) 1931.

roentgen findings. The stump of the lamina on one side was found to dip inward and impinge on the cord. Laminectomy was performed with complete relief of symptoms.

[ED. NOTE.—The finding of connective tissue bands, lipomas and other pressure-making complications of spina bifida occulta is more extensively reported in Europe than in this country. Abroad also more stress is laid on the spina bifida occulta as a cause of clubfoot, contracted tendo achilles and other deformities. Whatever the rôle spina bifida may play in causing symptoms the foregoing case should be a warning to surgeons to ascertain carefully the anatomy when exploring such regions. To a less careful observer a lumbosacral fusion might have seemed a logical procedure and yet in this case it would certainly not have given relief.]

#### DISTURBANCES OF GROWTH

*Longitudinal Growth of Bone.*—Basing his conclusions on a compilation of the literature of the endocrine glands, Bergmann<sup>5</sup> reported that longitudinal growth occurred in jumps; the two main periods were the first few years of life and the period of puberty. During the remaining years growth was slower and more regular. Presumably the thymus was responsible for the first stage and the hypophysis and thyroid for the second. Loss of the thymus, thyroids or hypophysis caused marked dwarfism. Castration caused increase in length. Removal of the parathyroids seems to have no effect on length of growth. The author stated that the Heuter-Volkman teaching that pressure hindered growth and release of pressure increased it was not to be accepted without reservation. A number of experimental studies were recounted in which the number of animals was rather small. It was found that inactivity (enforced) produced but slight retardation of growth in length. The articular ends, however, were poorly developed. In operatively produced dislocations of the hip and shoulder new joints were produced by nature. A slight overgrowth in length observed in these cases was referred to the operative trauma as a stimulus of growth. Severance of the sciatic nerve gave no demonstrable change in growth in length. Arthrodesis of the knee stimulated the limb to overgrowth, as did ligation of the femoral vein. Periarterial sympathectomy and lumbar ramisection produced no measurable increase in length. By inserting needles in the midpart of the shaft of the long bones of young animals, growth at the ends could be measured. The epiphyses nearest the knee and farthest from the elbow were most active in adding length to the extremities. The lower femoral epiphysis was the most active center.

5. Bergmann, E.: Deutsche Ztschr. f. Chir. 233:149, 1931.

The two tibial epiphyses were about equally efficient. The forearm centers were three times as active as the elbow centers. Eleven tuberculous patients were interviewed after a lapse of years. In childhood each had had recorded an increase in length of the limb as a result of the presence of the tuberculous focus. At reexamination in adult life only one had retained his full lengthening over his normal limb. In two it had dwindled to one-half its former value. In three the limbs were now equal. In five an actual shortening was now present.

[ED. NOTE.—The important factor in disturbance of growth in tuberculosis would appear to be the age at which the lengthening of the limb was observed and how closely this approximated the closure of the epiphyses and the normal cessation of growth.]

#### DISTURBANCES OF CALCIUM METABOLISM

*Rôle of Hyperparathyroidism in Skeletal Dystrophies.*—Wolti<sup>6</sup> reviewed the literature dealing with the rôle of the parathyroid glands in diseases of the bony skeleton. He found three groups of diseases which has been considered at one time or another to be allied to parathyroid disturbance: 1. The first group consisted of generalized osteitis fibrosa cystica (von Recklinghausen's disease). Considering the frequency with which lesions of the parathyroids were found accompanying osteitis fibrosa cystica, it was logical to suppose that the disease was simply a manifestation of hyperparathyroidism. Certain apparent irrelevant findings could be accounted for by the presence of complicating factors. The cures following parathyroidectomy should not be confused with the temporary remissions seen in the course of osteitis fibrosa cystica and surgical intervention in regard to the parathyroids should be insisted on as in the severe forms of the disease all other treatment was ineffective. 2. The second group consisted of osseous dystrophies. No satisfactory evidence was found to connect hyperparathyroidism with either rickets, osteomalacia or Paget's disease. 3. In the third group was ankylosing polyarthritis (spondylose rhyzomélisque). Careful study showed that improvement seen in cases of spondylose rhyzomélisque following parathyroidectomy could always be logically explained as due to other factors than the operations. No evidence was found to show that in any case of ankylosing arthritis there was also a true hyperparathyroidism, although some of the symptoms of this condition might occasionally be found. The conclusions drawn were that parathyroidectomy was indicated in cases of multiple osteitis fibrosa cystica in which the existence of hyperparathyroidism could be shown to accompany the bony changes. Its existence was shown by diminution in muscle tone, hyperexcitability of nerves and muscles to

6. Wolti, M. H.: J. de chir. 38:633 (Nov.) 1931.

electric stimulation, general discomfort in the bones themselves, elevation in the blood calcium level and increased calcium elimination in the urine. Usually the hyperplasia of the parathyroids was not found until at operation, but occasionally a tumor could be palpated. Cystic disease alone without other signs of hyperparathyroidism was not sufficient indication for operation. Similarly, operation might be logically envisaged in a case of spondylose rhizomélisque if the case also presented the other signs and symptoms of hyperparathyroidism.

*Osteitis Fibrosa.*—In a careful review of the pertinent literature, Schupp<sup>7</sup> called attention to the necessity of not confusing the osteitis fibrosa of von Recklinghausen with the other obscure bone dystrophies which to date still constituted unsolved problems in respect to etiology. He reported two cases in point. The first was an unusual case of osteitis fibrosa cystica of von Recklinghausen in which a parathyroid tumor was demonstrated lying in the body of the thyroid gland. In this case marked cyst formation was not grossly apparent. Histologic study indicated that cysts had been present but had vanished as the result of spontaneous fracture. The first case thus was a proved case of hyperparathyroidism. The second case grossly might have been declared to be in the same category. Marked osteoporosis, cyst formation (large marrow cysts with giant cells) and spontaneous fractures were present. Yet postmortem examination of the parathyroid glands which were submitted to Schmorl for check-up revealed no hyperplasia macroscopically or microscopically. It was a case of marked senile osteoporosis. The author emphasized that to date there is no known cause for Paget's disease, and that histologic diagnosis of bone lesions on the basis of a single specimen was unreliable.

[ED. NOTE.—In view of the recent tendency to ascribe to the parathyroid gland syndromes which to date have no demonstrable pathologic association, namely, Paget's disease, senile osteoporosis, arthritis deformans and osteomalacia—such a reminder is worth while. It is to be expected that enthusiasm should overshoot its mark. The wholesale application has come not from the original describers who have checked their clinical findings by critical chemical and pathologic data but from well intentioned but uncritical clinicians.]

*On the Mode of Action of Viosterol.*—Bauer, Marble and Claffin<sup>8</sup> studied the effect of viosterol on calcium, phosphorus and nitrogen metabolism in normal persons and in certain pathologic states. The effects briefly summarized were: 1. The effects of small doses of viosterol (from 5 to 20 mg. a day) when given to normal adults on

7. Schupp, H.: Deutsche Ztschr. f. Chir. **253**:195, 1931.

8. Bauer, W.; Marble, A., and Claffin, D.: J. Clin. Investigation **11**:1, 21 and 37 (Jan.) 1932.

a diet either high or low in calcium were slight and not constant. 2. Large doses (30 mg. a day) under the same conditions produced an immediate increase in fecal calcium and phosphorus accompanied by a decrease in the urinary calcium and phosphorus. Later this change was reversed with absorption of more calcium and phosphorus from the intestine than normal and with a corresponding increase in urinary excretion. The calcium and phosphorus balances were not affected. The serum calcium and phosphorus levels were slightly raised. No changes in nitrogen metabolism were noted. No ill effects from the administration were noted. 3. A case of osteoporosis and another of osteomalacia were both greatly improved by the use of viosterol in conjunction with a diet high in calcium. The authors considered both cases as diseases due to calcium deficiency, and concluded that viosterol aided in the absorption and utilization of calcium and phosphorus if adequate amounts were given in the diet. They were able to demonstrate that cats previously on a diet low in calcium showed better bone trabeculation and more rapid deposition of calcium and phosphorus when fed viosterol and a diet high in calcium than when the diet high in calcium alone was used.

Aub and Farquharson<sup>9</sup> studied the phosphorus and calcium metabolism in various metabolic and bone diseases and were able to detect no gross variation from the normal in any case. Metastatic carcinoma, myeloma, "focal osteitis fibrosa" (bone cysts), fragilitas ossium, osteosclerosis, osteochondritis deformans juvenilis (Legg's disease), gout and chronic hepatitis with jaundice all gave negative results.

#### THE SPINE

*Paraplegia Associated with Nontuberculous Kyphoscoliosis.*—Viets and Clifford<sup>10</sup> reviewed the literature and reported an additional case of nontuberculous kyphoscoliosis associated with paraplegia. In their case there was poliomyelitis with a severe residual thoracic kyphoscoliosis which produced with gradual onset a typical complete spastic paraplegia. Partial subarachnoid block was demonstrated. Laminectomy was performed, the pressure on the cord was relieved, and the patient gradually recovered both sensory and motor power. They reviewed briefly the seventeen cases previously reported in medical literature. Five of the eight patients operated on were found to have an epidural fat pad at the site of the spinal angulation. Some of the patients treated conservatively by hyperextension improved or recovered, but surgical decompression was usually required.

[ED. NOTE.—It is important to consider the possibility of syringomyelia in cases of kyphoscoliosis associated with paraplegia.]

9. Aub, J. C., and Farquharson, R. F.: *J. Clin. Investigation* **11**:253 (Jan.) 1932.

10. Viets, H. R., and Clifford, M. H.: *New England J. M.* **206**:55, 1931.

NEOPLASMS

*Homogeneous Enostoses.*—Krauss<sup>11</sup> found that 4 in 12,000 roentgenograms of the skeleton disclosed homogeneous enostoses. The work of Virchow, Cruveillefand and M. B. Schmidt had placed this condition on an anatomicopathologic basis. These enostoses were divided into two groups, homogeneous and spongy. The former were visible in the shaft of the bone as oval or circular sharply outlined, dense shadows without integral structure being visible. The latter were irregularly bounded and spotted. One obtained the impression that the former were the end-stages of localized inflammatory processes whereas the latter was new growths of bone. Treatment might consist of multiple drilling with a fine wire drill (Beck) or resection (Bennecke). Pain might attract attention to the lesion, and it was relieved by extirpation.

*Therapy of Chondromatous Exostoses of the Pelvis.*—Two cases of chondromatous exostoses of the pelvis were reported by Walzel<sup>12</sup> in both of which cases the exostoses were resected. The first resection had been performed eight years before. In this case the pubis and ascending ramus of the ischium were removed. There was no hernia subsequently, but a diverticulum of the bladder became demonstrable eleven months after operation. In the second case the resection included the pubis from the symphysis to the acetabulum. Four weeks after operation the patient walked without discomfort. The author recommended radical excision in cases that had not responded to roentgen therapy.

[ED. NOTE.—In the experience of the authors this type of tumor does not respond to roentgen treatment; therefore, it would seem that immediate excision of such new growths would be indicated. From the surgical standpoint the article is interesting in that it demonstrates that a large portion of the pelvis may be removed without serious disturbance of function.]

*Fibrocartilaginous Tumors of Bone.*—Over 500 tumors of the skeleton were analyzed by Geschickter<sup>13</sup> and were divided into the following three groups: (1) osteochondroma, benign exostoses, (2) chondromas and (3) chondromyxosarcomas, the latter being a form of osteogenic sarcoma containing cartilage. The clinical features, incidence, roentgenographic findings, pathology, histogenesis, etiology, treatment and prognosis were discussed in detail. In regard to the benign tumors of the first group, the author warned that their removal was usually accomplished in too careless a manner. Five per cent of them in

11. Krauss, F.: Zentralbl. f. Chir. 58:3132 (Dec. 12) 1931.

12. Walzel, P.: Deutsche Ztschr. f. Chir. 233:327, 1931.

13. Geschickter, C. F.: Fibrocartilaginous Tumors of the Bone, Arch. Surg. 23:215 (Aug.) 1931.



this series recurred and in over 7 per cent a secondary malignant change arose. The latter high figure he believed due to more careful study than is usually given. Similarly, when dealing with tumors of the second group, there was a definite danger of transplantation of the tumor tissue in the wound with subsequent recurrence. When occurring in the small bones of the hand or foot (the os calcis excepted) they might be considered benign and curable by thorough extirpation. True chondromas of large size occurring about the sternum, spine and long bones must be regarded as potentially malignant, however, and their surgical removal followed by radium therapy. In dealing with the primary chondrosarcomas permanent cures were rare, and the disease even in spite of prompt amputation ran its course in about twenty months. The secondary chondrosarcomas were less rapidly fatal and the author's percentage of actual cures was 24.

The conclusions drawn were that the gradations in a single type of tissue differentiation met with in the three types of tumors implied a close relationship between the formation of the tumors and the general factors concerned in the growth and differentiation of body tissue. Apparently all these tumors had their origin in an early precartilaginous connective tissue and their degrees of malignancy were expressions of the rate and extent of differentiation in this tissue. When the rate of differentiation was slow and the extent of bone formation large, a benign tumor resulted. When it was rapid and adult cartilage and ossification was small, the tumor became malignant. In all the tumors the histogenic cycle was the same implying that the tissue of origin and not the etiologic agent was the important factor. Whether or not the rate and extent of differentiation that governs the degree of malignancy was predetermined in the tissue or whether it was dependent on the etiologic factor precipitating the growth, was not certain. It would seem, however, that the etiologic factor was of secondary and variable importance. Finally, the replacement "of connective tissue by cartilage, and of cartilage by bone, the order of which is adhered to in evolution in embryology and all the forms of benign and malignant tumors of the fibro-cartilaginous group, indicated an inherent and immutable sequence which prevailed in spite of the avowed lawlessness of tumor growth."

#### POLIOMYELITIS

Kramer and Aycock<sup>14</sup> studied a localized epidemic of poliomyelitis in the town of Bedford, Mass. Approximately fifty cases of mild diseases (headache, colds, fever and vomiting) occurred at the time of the epidemic among children attending school among the pupils of which

14. Kramer, S. D., and Aycock, W. L.: *Proc. Soc. Exper. Biol. & Med.* 29:93 (Oct.) 1931.

all the frank cases of poliomyelitis which occurred were studied. Five months later serums were taken from these children and compared with controls from the same town and from another town which had escaped the epidemic. Neutralization tests with poliomyelitis virus in vitro were identical in three groups. The authors concluded that "the widespread immunization of a population does not take place entirely at the time of an outbreak but rather in a more or less uniform manner throughout the year or in interepidemic periods." This agreed with the European theory that immunity was due to a nonspecific physiologic and serologic change accompanying maturity.

#### TUBERCULOSIS

*Specificity of Light Action in Experimental Tuberculosis.*—Luce-Clausen and Bayne-Jones<sup>15</sup> repeated, with certain minor variations, earlier experimental work of Phelps<sup>15a</sup> in 1930, and obtained diametrically opposite results. They found that guinea-pigs inoculated with a measured dose of tubercle bacilli and irradiated daily with the band of ultraviolet light (from 320 to 380 millimicrons) which Phelps claimed was specific, lived no longer than control animals kept in complete darkness. Infra-red radiation (from 720 to 1,120 millimicrons) used on a third group of animals, was apparently deleterious, as they did not live as long as the control group. Pathologically, the lesions of the three groups were identical in appearance.

[ED. NOTE.—There is as yet no uncontroverted evidence that any portion of the sun's spectrum has any specific effect on tuberculosis. It is difficult to separate the effects of heliotherapy on tuberculosis of the bone and joint from those due to rest, immobilization, adequate orthopedic care and other general factors.]

#### CHRONIC ARTHRITIS

*Statistical Study of Atrophic Arthritis.*—Smith,<sup>16</sup> in a study of 102 cases of atrophic arthritis, found the usual distribution in regard to sex. Most of the cases had had their onset in persons in the twenties or early thirties, and most of the patients were of the asthenic habitus. There were more persons of dark complexion than blonds. Occupations which involved exposure seemed to predispose. Blood and other laboratory studies showed no definite features, although they suggested usually a lowered general health.

15. Luce-Clausen, E. M., and Bayne-Jones, S.: *Am. Rev. Tuberc.* **24**:686 (Dec.) 1931.

15a. Phelps, W. M.: *J. Bone & Joint Surg.* **12**:253 (April) 1930.

16. Smith, M.: *New England J. Med.* **206**:103 (Jan. 21) 1932.

*Bacteriology of Blood in Chronic Arthritis.*—Bernhardt and Hench<sup>17</sup> made eighty blood cultures from twenty patients with infectious arthritis. The method of Cecil, Nicholls and Stainsby was used carefully with negative results in each case. They summarized the literature on the subject.

*Mixed Forms of Arthritis.*—Of 1,459 cases of chronic arthritis tabulated by Archer<sup>18</sup> and Cecil, 1 per cent showed evidence of both the proliferative and degenerative types. These mixed cases presented the typical lesions of each of the two types of disease except that proliferative lesions seemed to be less virulent and progressive than when seen alone. Thus a proliferative and degenerative process, each an entirely different pathologic condition, might appear in the same patient. Either of these processes might be the original one and the other the superimposed one. Therefore, while clinical and pathologic evidence tended to separate chronic arthritis into two main divisions there were borderline cases which embraced both types.

*Traumatic Arthritis.*—Key<sup>19</sup> enumerated the various types of chronic traumatic arthritis. Acute traumatic synovitis was not considered except incidentally in the discussion. Traumatic arthritis might follow: (1) a single severe injury to the articular cartilage, (2) repeated mild injuries, (3) disorganization of the joint mechanics and (4) bony deformity. Typical cases of each causative factor were discussed. Certain cases could be prevented. Medical treatment was of value only in that it affected the patient's general health and reparative powers. Physical therapy was of value and the greatest physical therapeutic aid was rest. Manipulation should be used with caution if at all. Surgical measures were indicated for correction of bad alignment (osteotomy), removal of foreign bodies, fusion (of certain joints only) and, in extreme cases, for arthroplasty.

(To be Concluded)

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17. Bernhardt, H., and Hench, P. S.: *Bacteriology of the Blood in Chronic Infectious Arthritis*, J. Infect. Dis. **49**:489 (Dec.) 1931.

18. Archer, B. H.: M. J. & Rec. **134**:344 (Oct. 7) 1931.

19. Key, J. A.: Arch. Phys. Therapy **12**:550 (Sept.) 1931.

# ARCHIVES OF SURGERY

VOLUME 25

OCTOBER, 1932

NUMBER 4

## THE PROCESS OF TENDON REPAIR

AN EXPERIMENTAL STUDY OF TENDON SUTURE AND TENDON GRAFT

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The process of tendon repair and the technic of tendon suture and tendon graft are two of the major problems of present day surgery. The thirty-eighth session of the French Congress of Surgery, 1929, devoted considerable time to the report of Bonnet and Bloch on the repair of tendons of the hand. This, in fact, was one of the three main subjects discussed, the other two being surgical intervention in

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Dr. Mason worked under a surgical fellowship granted by a friend who desires to remain unknown.

pulmonary tuberculosis and in Pott's disease. Despite many excellent experimental and clinical studies, there is little unity of opinion among qualified students regarding any of the major issues of the problem. The actual histologic process of the repair of divided tendons and of the healing of tendon grafts, the source of the tissues that make for union between tendon stumps and between stumps and tendon graft, has been, and still is, the subject of considerable controversy. The question of spontaneous repair is by no means obviously explicable, and its experimental study has led to several logical conceptions. The significance of the synovial sheath in the process of repair led to a controversy between Bier and his pupils and Rehn and his pupils which is still being waged. The scanty vascular supply of tendon tissue and the necessity of a good vascular supply to reparative tissue are two factors that appear to be constantly working against the surgeon. The force of this fact is more strongly brought out when it is remembered that adequate vascularization of grafted tissues, e. g., a skin graft, requires rest and immobilization, while rest and immobilization of injured tendons favor the formation of adhesions—the most important factor making for the failure of operations on tendons. Experimental and clinical observations have shown that function is of major importance in determining the histologic structure of tendon tissue, and emphasize the necessity for purposeful movements of tendons during the course of healing. The necessity of function during healing would seem also to be incompatible with the immobilization necessary to obtain efficient vascularization and secure union. The tension at which tendon should be sutured is a very definite and perplexing problem. While there is no doubt that freshly divided tendon should be sutured end-to-end, after relaxation has been obtained by bringing origin and insertion of the muscle as closely together as possible (Mayer), the problem is not so simple when one considers suture and repair of older injuries. Here the retraction is due not only to muscular tonus, but to intramuscular fibrosis as well, and while the former may be overcome, the latter is to a certain extent permanent, and end-to-end suture leads to permanent shortening of the tendon.

At the suggestion of Dr. Allen B. Kanavel, a series of studies of tendon surgery have been undertaken in the laboratory of experimental surgery of Northwestern University School of Medicine. Under Dr. Kanavel's guidance, it has been planned to study various aspects of the problem in an attempt to obtain, experimentally, first hand knowledge of tendon repair. The present report deals with a histologic study of healing tendons and tendon grafts.

#### HISTORICAL DATA

It is not surprising to one acquainted with tendon surgery that operative procedures on these structures found slight general favor

with the surgical profession until after the advent of antiseptic surgery. The ancient and medieval surgeons were handicapped not only by the lack of knowledge of wound infection, but also by the fact that it was not until the middle of the eighteenth century that clear distinction was made between tendon and nerve, despite the fact that Galen had described the differential anatomy of tendons, nerves and ligaments. Without doubt, the catastrophic possibilities of this lack of knowledge were enough to discredit most of the early operative repair of tendon wounds. There must have been many lacerating injuries of the hands and feet with which the older surgeons had to deal; still reports of tendon repair are meager and scattered.

Galen in the second century demonstrated the differential anatomy of tendons, nerves and ligaments, but warned against the ill results of tendon suture. This warning came from the fact that he considered tendon a mixture of nerve and ligament, and he considered that suture within nerve substance was likely to be followed by severe pain, twitchings and convulsions. It is not improbable that Galen had seen patients with median nerve injury at the wrist in whom the distinction between nerves and tendons had not been made and in whom suture was followed by symptoms of nerve irritation. Galen's influence was felt for nearly sixteen centuries.

The time between Galen and Haller, who demonstrated the specificity of tendon tissue, was not entirely barren. Avicenna in the tenth century strongly advocated tendon suture. It was somewhat over two hundred years later that the teachings of this Arabian physician were promulgated in Italy by Roger, Roland, Lanfranchi and William of Falicet. The last surgeon asserted that nature was unable to unite divided tendons, and that the surgeon could bring the stumps together better than nature. About the same time (early in the fourteenth century) the French surgeon, Guy de Chauliac, evidently under the influence of the Italian surgeons, attempted with but a modicum of success to defend the closure of tendon wounds.

Another two centuries elapsed before one reads in the works of Ambroise Paré in the sixteenth century of successful instances of tendon suture, and it is logical to assume that he himself had practiced it. Still there was no general acceptance of surgical procedures on tendons. The great Galen had said fourteen hundred years before that a prick of a nerve or tendon would lead to convulsions, and, without attempting experimental confirmation of this opinion, the surgical profession accepted this dictum as a fact.

During the seventeenth century a few experimenters reported successful tendon sutures on dogs. Lanzweerde divided the tendon achillis in dogs and sutured it. Healing occurred and full functional use of the leg returned. Nuck also made some experimental sutures with success.

Meekren (1682), nearly seventy-five years before Haller, tested crudely the sensitivity of tendon tissue to injury. He found no evidence that the tendons were sensitive or that the pricking or injuring of them caused pain. In the domain of clinical surgical intervention, however, tenorrhaphy was still in disrepute. The maxim never to pass a needle through a tendon had such a great hold on the profession that one surgeon (Bienaise, in dealing with a wound in the palm), instead of suturing, wrapped the suture around each end of the divided tendon and then tied the sutures together. (Curiously enough, in the case reported a good result was obtained.)<sup>1</sup>

It was not until after Haller in the middle of the eighteenth century, demonstrated that tendons were insensible, that operative procedures on them were to become generally accepted. Even then it took nearly two generations finally to eradicate the teachings of Galen, and it remained for Strohmeier and Dieffenbach (1831) really to popularize the rather simple operation of tenotomy for clubfoot.

The actual process of tendon repair, in which we are particularly interested at present, was apparently first studied experimentally in dogs by Hunter in 1767. According to Hunter, tendon heals by the formation of callus, produced in much the same manner as is bone callus. V. Ammon, in 1837, considered that the defect left by tendon injuries was first filled by a formless exudate, and that later the tendon stumps themselves regenerated the new tendon. Bouvier and Velpeau, on the other hand, considered that the new tissue owed its origin mainly to the sheath tissues about the tendon. Paget noted that the tendon defect was first filled with a fluid exudate; this was then replaced by fibrous tissue which gradually took on the appearance of tendon.

It was the significance of the fluid exudate (blood) that first attracted the attention of Pirogoff. According to him, the blood exudate was the *conditio sine qua non* for tendon repair; it not only stimulated the surrounding tissues, but furnished some of the material for the new tendon. Without the exudate an incomplete scar and no, or poor, union occurs. With the exudate the regeneration is good. The material for the formation of the new tendon comes not only from the exudate, but mainly from the sheath tissues about the tendon and to a slight extent from the tendon stumps themselves. Bouvier agreed with Pirogoff, as did also Thierfelder, Boner, Feltz and Dembowski after experimental studies. Billroth, however, asserted that the exudate in reality hindered growth of the scar, in that absorption must take place and thus delay the union. Billroth's position was strongly supported by Adams, whose experimental work is not widely known. The question of the value of this exudate and the part it plays appear even in later studies of tendon

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1. The preceding historical résumé was found in an editorial by an unknown writer which appeared in M. J. & Rec. 127:156 and 213, 1928.

repair. Thus one finds that Vierung in an excellent experimental paper asserted that without exudate regeneration does not occur. Other writers mention the exudate, though the view taken is that while it hinders healing, its value, in the main, is that of keeping open the defect so that regeneration can take place.

Dembowski believed that the new tendon was formed by cells that wandered into the defect from the blood. He based his conclusions on the observation that cells in the new tendon contained a dye that had been previously injected into the blood stream.

Bizzozero asserted that the new tendon was formed by the connective tissues that surrounded the stumps and that the sheath and stumps played only a minor rôle.

Güterbock partially divided tendons and found that the defect was first filled by a bit of the sheath falling into it. At the end of twenty-four hours, proliferative changes were noted in the sheath and surrounding connective tissue. The sheath played the greater rôle. By the end of three days these defects were entirely healed, and after the first week the number of mitoses was already fewer, and after several weeks the cell content was much reduced. Although the tendon played no rôle, or a very minor one, in this process, Güterbock did find proliferative changes among the tendon cells themselves, following the irritation caused by drawing a thread through the tendon.

According to Beltzow, the tendon stumps take some part in the new formation of tendon and in the organization of the scar. The intervening tissue between the stumps, however, is essentially a scar, since it tends to retract. Despite the marked histologic resemblance to tendon, the new tissue is not a true regeneration.

Vierung believed, after an experimental study in which he used the tendo achillis of the rabbit, that the peritendinous and intratendinous connective tissues were the main sources of material for the organization of the tendon scar. Tendon cell mitoses were seen to be present, but not until the fourth day, and it was assumed that their participation in the process was of minor importance. Vierung was the first to note that under the influence of function the nuclei and fibers of the tendon line up in rows parallel to the line of pull, while if this functional stimulus is absent, the new tissue remains disorderly and nonoriented.

Busse agreed in the main with Vierung. He said that the blood exudate was gradually replaced by granulation tissue which must come from the peritenonium externum and internum. He found also that the tendon cells proliferated, but only later and in a disorderly fashion, entirely dependent on an increased vascularity, and that as the vessels diminished in number, the mitoses disappeared.

Enderlen's study of the reparative changes in the tendo achillis of the guinea-pig demonstrated the importance of the tendon cells them-



selves in the regenerative process. He showed that healing of the tendon wound is due to proliferative changes on the part of the tendon, of the peritenonium internum and externum and to some extent of the surrounding connective tissue. At first, there is a blood exudate in the gap, and the peritenonium externum falls into the wound. Some degenerative changes are seen in the ends of the stumps, i. e., swelling of the fibers, breaking up of the nuclei and leukocytic infiltration. By the second day, regenerative changes appear; mitoses are found in the tendon in great number, as well as in the internal and external peritenonium. These tendon mitoses are not dependent on proximity to blood vessels, but are frequently seen at some distance from the vessels. Some connective tissue cells, many in process of mitosis, are present in the blood exudate. By the fourth day proliferating tendon cells are found pushing into the defect, and by the sixth day tendon fibrils appear among the nuclei and form with such rapidity that by the ninth day union of the stumps is effected. These fibrils at first are arranged without any order, but as union progresses and the pull of the gastrocnemius makes itself felt, they become more and more oriented in parallel rows along the line of tendon pull. A point that Enderlen makes and that is later emphasized by Borst and is noted also in our study is that the proliferation of tendon occurs fairly generally throughout the stumps and is not confined to a narrow zone at the line of division. After the fifteenth day, Enderlen noted that the proliferation slows up, and that as time goes on the number of nuclei and vessels diminish, the fibrils become oriented in longitudinal parallel rows and the new tissue takes on the appearance of normal tendon from which it can be differentiated with difficulty.

Marchand reviewed Enderlen's actual microscopic sections and came to a somewhat different opinion as to the nature of the process. According to this pathologist, most of the new tissue came from the sheath and surrounding connective tissue. At first the proliferating tissue is definitely demarcated from the stumps, but it soon pushes into the ends of the stumps, and it is difficult, probably impossible, to distinguish between tendon cell mitoses and connective tissue cell mitoses. Marchand did not deny that the tendon cells proliferated, but he did not believe that they took an important part in the process of tendon repair. The early irregular arrangement of the tissues filling the defect spoke for its varied origin. Marchand did say, however, that it made no great difference whence the tissue came, since it eventually produced a structure functionally equivalent to tendon.

Schradick believed that normal tendon does not form in a tendon defect, but that this is filled by connective tissue brought in by the surrounding tissues following retraction of the stumps. Although he noted mitoses of tendon cells, he considered them to be due to hyperemia

and not to any particular regenerative power on the part of the tendon. The new tendon, he noted, gradually became oriented and arranged in a long, rounded strand resembling normal tendon.

Seggel studied tendon suture experimentally in guinea-pigs and concluded that the sheath with surrounding connective tissues and the tendon took part in the process of healing. At first the gap left by division of the tendon is filled by a blood exudate, while some slight degeneration occurs in the traumatized ends of the stumps. The blood exudate is soon organized by connective tissue coming in from about the stumps and from the interstitial tissues of the tendon stumps. By the fifth day, the tendon has become hyperemic and mitoses appear first on the cut ends, and by the sixth day within the substance of the tendon at some distance from the divided ends. The gap is first filled by granulation tissue which is soon infiltrated by the proliferating tendon cells that gradually replace the connective tissue. By the twenty-ninth day, continuity is completely restored, and from then on the number of nuclei diminish, so that by from the seventieth to the eightieth day the tendon looks very much like normal tendon.

Borst's exhaustive and critical study of tendon regeneration substantiates Enderlen's views. Borst showed that the scar that fills the defect comes from several sources: the tendon, the peritenonium internum and externum and the surrounding connective tissues. The blood exudate in the gap is first infiltrated by polymorphonuclear leukocytes, later by fibroblasts and by the fourth day by proliferating tendon cells. From the fourth day on, Borst found that the course of healing varies and that the evaluation of the parts played by the various elements entering into the process was quite difficult. He stated that the factors on which the further course of healing depends are numerous and vary within wide limits. Thus the nature of the operative procedure, the presence of chemical irritants, infection, suture material, etc., influenced the healing process. Borst studied with especial care the tendon nuclei and chromosomes, and believed that he was able to distinguish proliferating tendon cells from connective tissue cells, and stated that even though ordinary scar may come to resemble tendon very much, the distinction can be made.

Following the time of Borst, the attention of investigators has been directed especially toward two aspects of the problem. One of these is the question of the importance of function in the healing of tendons, and the other is the significance of the sheath in the process. Barfurth, Solger and Roux had noted the importance of stress and pull on the formation of a tendon or tendon-like tissue following tendon division, and maintained that they were important factors in tendon regeneration. Ribbert, on the other hand, asserted that function played a minor part,

that each tissue had the innate power to reproduce itself and that, regardless of function or tension, tendon proliferation resulted in the production of tendon.

This question of the effect of function on tissues led to considerable experimental study of grafts in tendon defects. Kirschner made an experimental study of autoplasmic tendon and fascial grafts and found that tendon, whether subjected to function or not, remained alive, at least partly, but tended to lose its orderly parallel structure. He found that fascia also remained alive and that if subject to function, took on the character of tendon. Kirschner's experiments were corroborated by numerous others, among whom may be mentioned Ritterhaus, Dawis, Chiari, Denk, etc.

Rehn carried the experiments further and studied the effect of transplantation on all sorts of tissues grafted into tendon defects or into other places where they were or were not subjected to function. Rehn demonstrated that a tendon graft without function underwent retrogressive changes and practically disappeared, while, if subjected to function and placed under tension, not only did the graft remain viable, but it became attached in its location and replaced efficiently the lost tissue. He showed that success in the grafting of tendons depended on preservation of the external peritenonium, since this gives rise to the tissues that welded the grafts and stumps together, and, since it is less highly specialized and of a less dense structure, makes vascular connections more easily with surrounding tissues and maintains viability of the graft. Rehn experimented also in the grafting of nonspecific tissue into tendon defects and into other locations in which they were subjected to pull and stress. He found that these tissues took on tendon-like character and concluded that there was a metaplasia into tendon. Later, he modified somewhat his original conception of a true metaplasia, though he did show that the tissue very strongly resembled tendon. It was stated in objection to Rehn's conclusions as to the value of function that, since casts were applied to the part after tendon transplantation, there was no functional stimulus, and that regeneration was due to the inherent regenerative powers of the stumps. Rehn showed, however, that even under a cast the immobilized muscles were still active, and that they showed movements which acted as a functional stimulus on the graft.

The presence of a synovial sheath about a tendon may modify considerably the process of healing. Clinical experience has shown by abundant examples the very mediocre healing power of both tendon sutures and tendon grafts within a synovial sheath, especially in the absence of a good mesotenon or when the sheath is entirely surrounded by a dense osteofibrous tunnel. Bier and his pupil Salomon believed

that this was due to the presence in the synovial fluid of a hormone that inhibited tendon regeneration, and that if the sheath were left open so that the tissue juices could in some way neutralize the hormone, healing would take place by true tendon regeneration. This view was strongly contested by Rehn and numerous others. Wehner's experiments in particular are cited in contraversion of Bier's ideas. Wehner excised the patella in dogs and sutured the patellar tendon across the open knee joint where the suture line was constantly bathed in synovial fluid. Despite this, there was perfect regeneration of the tendon.

Hueck studied experimentally in dogs the problem of tendon regeneration within sheaths. He sutured the flexor tendons of the toes in the ball of the foot where they are contained in synovial sheaths. In some instances, the sheath was carefully closed over the tendon suture, while in others, it was left open or a part was cut away. He found that even when good apposition was obtained at operation, the stumps soon separated, and when examined at varying intervals afterward were found to be covered by a very small cap of tissue. This cap came from the thin external peritenonium. It appeared from the results of Hueck's experiments that it made no difference whether the sheath was open or was carefully closed, the cause for failure was apparently the lack of connective tissue capable of proliferation. A lack of blood vessels to the tendons did not apparently impress Hueck as important, except so far as these would be surrounded by connective tissue that could proliferate and lead to union.

Schwarz' exhaustive experimental study of the healing of tendon wounds and the plastic replacement of tendon defects is classic. His paper deals first with the anatomic process of tendon regeneration, its causes and prerequisites. Schwarz worked with the achilles tendon of the rabbit. In some instances the tendon was divided and not sutured, while in others it was sutured; in some the peritenonium (paratenon in this case) was left intact, while in others all of the paratenon and as much as possible of the subcutaneous tissues were excised. He concluded that the paratenon, when present, proliferated to fill the defect, but that this replacement tissue (*Ersatzgewebe*) is not as functionally efficient as normal tendon, since it tended to lengthen out. Schwarz found that the peritenonium internum also proliferates, but to less extent than the paratenon and only begins to do so about the sixth day, while the tendon cells are quiescent and take no part whatever in the formation of the replacement tissue. The replacement tendon at first is quite nuclear and very vascular, but it gradually loses nuclei and vessels; its irregularly arranged fibers condense and line up in the direction of pull of the tendon, and the nuclei become flat or oval. No matter, however, how much the replacement tendon may resemble normal tendon microscopically, it never does so macroscopically; its

normal mother-of-pearl sheen never returns. The presence of a suture did not change the fundamental basis of the process of healing. A suture kept the ends together better, but, as a matter of fact, did not entirely prevent their separation. Removal of peritenonium externum and as much as possible of surrounding connective tissue emphasized the importance of these tissues in the process of regeneration, since in this case even when the stumps were sutured the gap was not bridged across, the ends retracted, and the proximal stump nearly always became adherent to the surrounding tissues. Schwarz found that when the nerve supply to the muscle is divided the tendon wound heals, but that the tissue is a loose fibrous scar which does not in any manner resemble the replacement tendon (*Ersatzsehne*), which forms under the stimulus of function.

Schwarz conducted also a number of experiments with grafts, both of tendon and of other tissues, in the repair of tendon defects. In these experiments, he removed from the defect all tissue capable of proliferation and replaced the excised tendon by another tendon plus its external peritenonium. He found that the regeneration here was due to the external peritenonium, which was seen in active proliferation during the very first days. It establishes vascular connections easily with the surrounding tissues and forms a dense envelope about the grafted tendon. The tendon itself becomes partly necrotic, though the more peripheral parts of it remain viable; however, he believed it played a passive and rather unimportant rôle, even though a few mitoses may be seen. According to Schwarz, some other tissue, such as fascia, which is able to establish vascular connection more easily with the surrounding tissues, would serve better as graft.

Hauck believed that tendons heal by the formation of scar tissue due to proliferation of the peritendinous connective tissues. A good blood supply is necessary for good healing, and Hauck noted that, even in the case of tendons surrounded by a sheath, healing may occur provided a good mesotenon is present. The scar resultant from healing is never replaced by, or transformed into, true tendon. The tendon itself plays no part in the actual repair.

Salomon, a pupil of Bier, studied the process of tendon repair and suture within a sheath. According to him, the poor healing power of tendons enclosed within a sheath are due to two factors. One of these is the synovial fluid which inhibits growth probably through a hormonal action and certainly in that it keeps connective tissue away from the area. The other factor is a paucity of tissue capable of proliferation. Tendon heals essentially by the proliferation of the peritenonium externum and internum. In cases of tendons not enclosed in a sheath, the paratenon furnishes an abundance of tissue capable of proliferating.

In the case of sheath-covered tendons, the synovial layer covering the tendon is very thin and can proliferate poorly, and the peritenonium internum is also scanty. Salomon did find, however, that by performing tenotomy above the sheath and by suturing the tendon within the sheath union would occur. This union, however, was dependent on securing a close suture which held the stumps well together, since otherwise too great a gap would result for the scanty regenerative powers of the tendon to bridge. He suggested an intravaginal suture leaving the sheath open or excising parts of it in order to allow the suture line to come into contact with the subcutaneous tissues.

Imayoshi's experiments with vital staining tend to bear out Borst's and Enderlen's position—that the healing of the defect is due to tendon cell proliferation. This investigator believed he was able by a method of vital staining (Kiyono) to distinguish between tenoblasts and fibroblasts. The tenoblasts come from the stumps, not directly on the line of tendon division, but slightly removed therefrom; they never come from connective tissue cells and never form by metaplasia from other cells. The first tissue to fill up the gap is fibroblastic; this, however, is later replaced by tendon cells.

Migliavacca, from an experimental study of tendon wounds of the tendo. achillis in rabbits, found that the tendon cells were actively proliferating by the third day, and that they could be seen penetrating the gap. These cells have abundant protoplasm, large nuclei and lightly colored intermediate substance, and the tissue they form becomes differentiated into new tendon tissue. These new cells or tenoblasts take the principal part in the formation of the tendon callus. By the fifth to the sixth day they begin to assume the appearance of tendon cells with elongated nuclei; by the tenth day fibrils arise in their protoplasm, and by the thirtieth day they have become regularly arranged in long parallel rows.

Max Lange's critically planned experiments have led him to conclude that the regenerative power of the tendon itself is not great. He found that if the external peritenonium and subcutaneous tissues were prevented from entering into the formation of the tendon callus, "tendon regeneration" did not occur. He did not question that tendon cells may regenerate, but he did not lay any stress on this regeneration in the process of tendon healing.

Bloch and Bonnet, in a long report on tendon surgery of the hand before the French Congress of Surgery in 1929, agreed in the main with Schwarz that the tendon callus is a replacement tendon and not a true tendon. The "Ersatzsehne" can always be differentiated from true tendon, and it is a question whether the tendon cells take any but a very minor part in its formation.

## EXPERIMENTAL DATA

## STATEMENT OF PROBLEM

The repair of tendon defects apparently depends on the proliferation of tissue from several sources. The problem is to determine the interrelationship of the different proliferative processes and their significance as regards the final result of a tendon suture or a tendon graft. Does repair of the defect come about mainly as the result of reparative powers of the connective tissue elements in and about the tendon? Do the proliferative changes noted within the tendon itself contribute toward the final result? Do both of these processes have definite and distinct functions in tendon repair? What is the practical surgical application of a knowledge of this repair?

## GENERAL OUTLINE OF EXPERIMENTAL WORK

In the present series of experiments sixty-nine dogs were operated on. In thirty-five of these, a tendon was divided and immediately sutured. In thirty-four a segment of a tendon was excised and immediately replaced by a segment of another tendon from the same dog. Certain of these dogs were allowed free and full use of the extremity immediately following operation. In others, the leg operated on was immobilized in a plaster cast for varying periods of time following operation. At various intervals after surgical repair of the tendon the legs were examined, the operative field exposed, and the tendon removed for microscopic section and study. In a few experiments the presence of a gross infection led to a discard of the material; in a few instances material was lost; in all, however, thirty specimens of suture and twenty-nine of graft were examined microscopically. It is on the results of these microscopic examinations that this report is based.

PROCESS OF TENDON REPAIR AS REVEALED BY  
EXPERIMENTS WITH TENDON SUTURE

## TECHNIC OF EXPERIMENTS

Experiments with tendon suture were performed on thirty-five dogs. In all experiments the tendon corresponding in man to the extensor carpi radialis (which is a double tendon) was divided and immediately sutured. The type of suture, with the exception of dogs S 6 to 16, inclusive, was the usual type of lacing suture used by Kanavel and Koch. In dogs S 6 to 16, an attempt at a splicing suture was made, in that a small segment was cut from the side of each stump, left attached to its mesotenon and placed in the gap as a sort of pedunculated graft. In the first five sutures of this type no tension suture was used; in the second five a tension suture accompanied the usual fine apposition sutures. The treatment accorded the sheath also varied somewhat in the different experiments. In dogs S 1 to 6 and in S 9, the sheath was split longitudinally and closed; in dogs S 21 to 35, it was split longitudinally and not closed; in dogs S 7 and 8 and S 10 to 13, the sheath was slit transversely and sutured, and in S 14 to 20, it was slit transversely and not sutured. Immobilization was not attempted in dogs S 1 to 16, while in S 17 to 35, a plaster cast was placed on the leg to secure maximum relaxation of the tendon.

## PROTOCOLS OF EXPERIMENTS WITH TENDON SUTURE

FOUR DAYS.—*Dog S 35.*—The tendon was divided and brought together satisfactorily with a lacing suture, and a cast was applied to keep the leg flexed and the radiocarpal joint extended.

The area of suture was examined on the fourth postoperative day. Healing had occurred per primum. The tendon ends, still united by the suture, had separated 1.5 cm. and were covered by hemorrhagic and edematous tissue. Union appeared to be due mainly to the surrounding tissues, since, although a pull of 11 pounds (5 Kg.) did not break through it, it broke easily with a slight pull after the peritendinous tissues were divided.

Microscopic examination of a cross-section of the proximal stump showed it to be badly disrupted by the suture material about which was seen some tendon degeneration. The tendon itself showed no evidence of proliferation, although the nuclei were possibly slightly larger than normal. The fibrous septums were thicker than normal. Along the borders of the tendon, the sheath was thickened and was fused to the tendon. The gap was filled with granulation tissue. The distal stump showed practically no change in the tendon cells. The fibrous septums, however, were thickened, and there was an increase of cells about the intratendinous vessels.

SEVEN DAYS.—*Dog S 34.*—This was a fairly satisfactory suture. A cast was applied. The wound healed per primum. The stumps had separated approximately 1.5 cm. and the suture had pulled out of the proximal stump. There had been proliferation of the sheath and peritendinous tissues, but none, so far as gross examination could determine, in the stumps.

Longitudinal sections of the distal stump microscopically showed little change in the tendon, except that due to the disruption caused by the silk. However, at one place, the nuclei in the tip were increased in number, and where the tip joined the intervening tissues it fused with them so that definite delimitation was absent. The sheath tissues about the stump were thickened and dipped into the gap to form a strand that extended toward the proximal stump. The gap tissue was made up of the proliferated sheath in which most of the fibers and nuclei were arranged in longitudinal rows parallel to the tendon pull. There was a moderate leukocytic infiltration about the silk suture.

A cross-section through the proximal stump showed few changes, except a thickening of the fibrous septums.

*Dog S 24.*—On uncovering the operative area, it was found that there had been a separation of about 2 cm. bridged across by fibrous tissue which successfully transmitted the pull. The newly united tendon appeared to glide easily through the surrounding tissues.

A longitudinal section through the whole specimen showed a union of the two stumps effected by the proliferated sheath tissues, which, passing over the stumps, dipped into the gap and formed there a dense strand. In this strand the fibers and nuclei were lined up in rows parallel to the line of pull of the tendon (fig. 1 *D*). The proximal stump showed an increase in number of nuclei in scattered areas throughout, and at the end of the stump the tendon fibers were seen to pass into a triangular zone of tissue which covered the tip and lay between the proliferating sheath tissues which dipped down about the stump to lie in the gap. This triangular zone (fig. 1 *B*) was made up of granulation tissue in which an orientation of fibers was already taking place. The intratendinous vessels were wide and dilated, and there was an increase of cells about them. The septums of the tendon were also thickened and more cellular than normal.



The distal stump also showed some proliferative changes. There was some increase in the number of nuclei even at some distance from the suture line (fig. 1 C), though the changes here were certainly less advanced than in the proximal stump. The sheath about the stump was thick and dipped over the end of the stump into the gap, where it fused with the proliferated sheath tissues from the proximal stump. The small triangular zone at the tip was disorganized and had not been invaded by fibrils from the stump.

*Dog S 33.*—A nice approximation was obtained, and a cast applied. The dog was killed seven days later. There had been some separation of the stumps, and the gap had been bridged across by fibrous tissue. A pull of  $2\frac{1}{2}$  pounds (1.1 Kg.) broke through the union just distal to the tip of the proximal stump.

Microscopic examination of cross-sections of the proximal stump showed considerable disruption of the tendon fibers, evidently due to the trauma of suturing. There was considerable thickening of the fibrous septums and sheath, and in places it was quite difficult to be certain that areas that looked like fibrous tissue were not in fact proliferating tendon. The gap tissue was apparently entirely granulation and fibrous tissue, presumably from sheath and peritendinous tissue proliferation.

*FOURTEEN DAYS.*—*Dog S 7.*—A splicing suture was used without tension suture, and the sheath was closed with plain catgut. No cast was applied. Fourteen days after operation the area was again exposed. The tips of the stumps were covered by dense adhesions which involved the deep fascia of the leg.

Microscopic examination showed that the tendon nuclei in the proximal stump had increased considerably in number. This increase was noted particularly in the tip of the stump, but was also present well up the stump as two broad nuclear strips. The increase in vascularity and fibrous septum proliferation noted in early specimens was seen here also. From some parts of the end of the stump, young tendon fibrils and nuclei could be seen to push distally into the gap. The sheath about the stump was thick and ran continuously from one stump to the other.

The gap between the two stumps was filled by a rather dense fibrous tissue in which were embedded the two segments of tendon tissue used originally to help splice the gap. In general, the tissues were lined up in rows parallel to the line of pull of the tendon, though the closer one approached the distal stump, the less definite this orientation became. Blood vessels were rather plentiful. The two bits of tendon included in this region were both alive and very nuclear and fused with the surrounding tissues. Mitotic figures were plentiful in these bits of tendon.

The distal stump did not end quite so abruptly as it had in earlier specimens. It showed instead considerable increase in the number of nuclei and many mitotic figures, especially at the tip; it passed over imperceptibly into the gap tissues. The fibrous septums were more nuclear and thicker than had been noted before in the distal stump. The sheath tissues had fused with the sheath from the proximal stump.

*Dog S 17.*—The divided tendon was easily and accurately sutured without an excess of tension. A cast was applied. The area of suture was again exposed two weeks later, and the specimen excised. The area of suture was easily uncovered and was not adherent to the fascia. The stumps had separated 2.2 cm. since suture, and were united by a small fibrous-like cord. The proximal stump was slightly bulbous. The distal stump looked gray and necrotic at the tip. The stumps and gap were covered over by a thin, shiny membrane.

Microscopic examination showed that the gap had been bridged across by the sheath and peritendinous tissues which had fallen into the defect and formed a dense strand from stump to stump. The tendon itself in the proximal stump showed

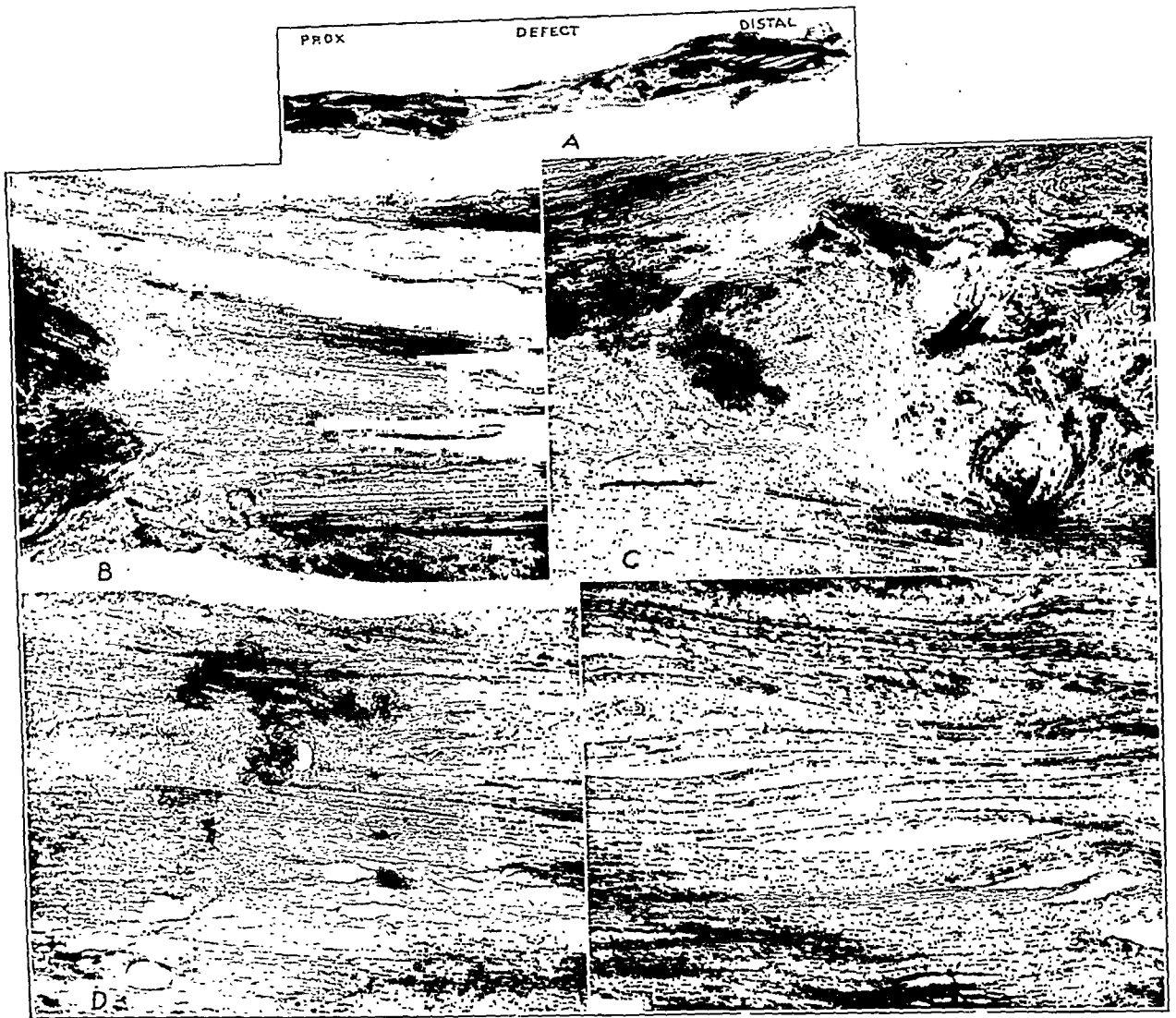


Fig. 1.—Sections through specimen S 24, which show the changes at the end of one week. *A*, entire specimen under very slight magnification. The proximal stump (*Prox.*) is thickened, and its sheath has spread distally over the end into and across the defect to meet the proliferated sheath tissues from the opposite stump (*Distal*). The ends of both stumps are clearly visible. *B*, the end of the proximal stump;  $\times 13$ . The stump ends very distinctly against the triangular area of tissue contained between the converging layers of the sheath, which are lining up in long parallel rows of fibers. *C*, the tip of the distal stump, is very much disrupted by the silk suture material which certainly interferes with the growth of tendon fibers proximally. *D*, the tissue from the central part of the defect, composed mainly of longitudinally arranged sheath tissues. *E*, a section taken from the distal stump, somewhat back from the end. This shows the straightening out of the fibers and the increased nuclearity of the tendon. A blood vessel with increase in tissues about it is also shown.

evidences of proliferation throughout the whole area of the section. The increase in number of nuclei was so great in places that the collagen fibers were either obscured or had disappeared, and mitotic figures were plentiful. At the end of the stump, the nuclei became much more numerous and the tendon fibers less and less distinct; a general transition occurred between the stump and the intervening tissues.

The gap tissue was made up of proliferated sheath and peritendinous tissues, with the addition of fibers from the proliferating tendon. Toward the middle of the gap, the uniting tissue became very thin, only to widen out again as the distal stump was approached.

The distal stump showed approximately the same picture as the proximal stump, except that it was not so far advanced.

*Dog S 6.*—In this dog, the tendon was sutured by means of a splicing suture, without the use of tension suture. A cast was not applied.

Examination on the fourteenth postoperative day showed that few adhesions had formed between the suture line and the surrounding tissues. The stumps had separated approximately 3 cm., and were united by rather soft-looking young connective tissue in which were embedded the two bits of tendon that had been excised from the stumps and used to splice the gap. The stumps and gap were covered by a paratenon-like sheath.

Microscopic examination was unsatisfactory, owing to the fact that the specimen had been partially dissected. Both stumps showed marked nuclear proliferation, tendon cell mitoses and partial fusion of their fibers with the gap tissues. The gap was filled by an organizing granulation tissue, by the proliferated sheath and to some extent by fibers coming into it from the tendon ends.

*Dog S 14.*—A splicing suture and tension suture were used. No cast was applied. The specimen was removed two weeks after operation.

Microscopic examination showed that the stumps were held together by proliferation of the sheath tissues and mesotenon, which formed thick strands passing from one tendon end to the other. The cells and fibers in the uniting tissues had lined up in parallel rows along the course of pull of the tendon. Neither stump showed marked proliferation; there was an increase in the number of nuclei, however, and mitoses were present.

*Dog S 15.*—The procedure in the experiment was practically the same as that described for S 14.

Microscopic examination showed that the whole specimen was diffusely infiltrated with leukocytes. In the proximal stump, the fibrous septums were thick and nuclear, and many mitoses were seen. The tendon itself was much more nuclear than normally, especially toward the tip, where the nuclei were so numerous as to obscure the collagen fibers. Many mitoses were seen scattered throughout. At the end of the stump, the tendon tapered off gradually, still maintaining its increase in nuclei, and fused imperceptibly with the gap tissues. Suture material embedded in the stump was surrounded by inflammatory infiltration with occasional giant cells.

The tissue in the gap was made up in the main of sheath proliferation. The most proximal bit of splicing tendon was alive and showed about the same proliferative changes as the proximal stump with which it had fused. The nuclei were increased in number, fatter and more vesicular than normal, and numerous mitoses were seen. The gap tissue more distally was made up of granulation tissue, centrally about which was the fibrous sheath.

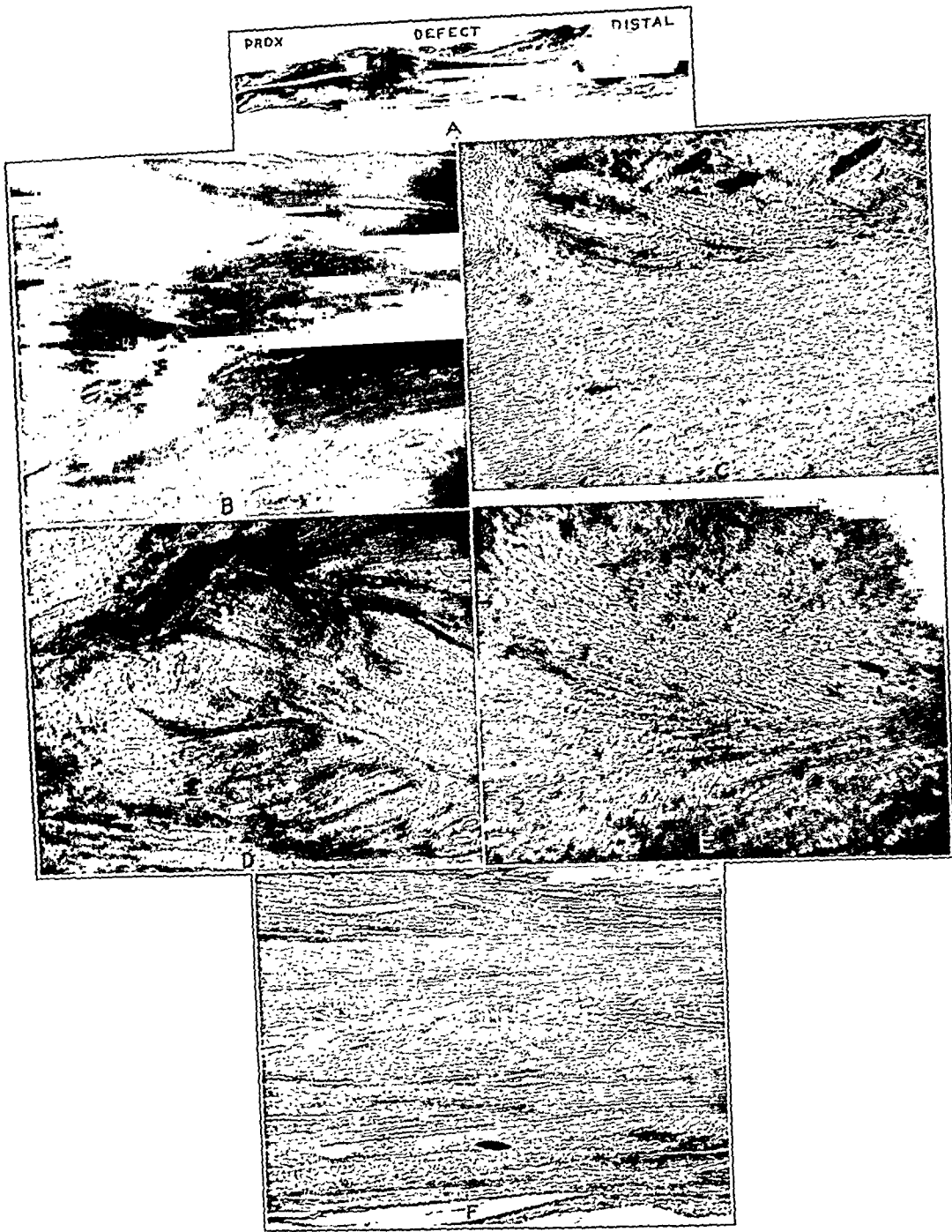


Fig. 2.—Sections through specimen S 22 showing the progress of healing at the end of the second week. *A*, the bulbous tip of the proximate stump (*Prox.*), has proliferated and sends fibers distally into the gap with which it fuses, without a definite zone or line of boundary between tip and intervening tissues being distinguishable. The distal stump also is beginning to proliferate, and, while more definite and distinct than the proximal stump, is also beginning to fuse with the tissues in the defect. *B*, the tip of the proximal stump. Here the proliferated fibers from the stump are continuous with those of the defect, and, as shown in *C*, no delimitation is possible. *C*, the end of the proximal stump at the place where it passes over into the gap. *D*, the end of the distal stump. Despite disruption by the silk, the tendon is proliferating, there is great increase in number of nuclei, and the tendon is spreading out fanlike into the intervening tissue at its tip. *E*, the end of the distal stump, showing the fanlike spread of the proliferating tendon; reduced from a magnification of  $\times 45$ . *F*, section, reduced from a magnification of  $\times 12$ , of tissues from the central part of the defect. This shows the sheath tissues forming a strong, well oriented, fibrous union.

The distal stump also showed evidences of tendon cell proliferation, especially about the periphery, where it had fused with the gap tissues. There was slight inflammatory infiltration about the silk suture. The sheath about the stump was thick and vascular and fused with the gap tissues.

*Dog S 22.*—An end-to-end suture was done under considerable tension in this case. A cast was applied.

Microscopic examination (fig. 2) of the proximal stump showed so much nuclear proliferation that the eosin-staining collagen fibers were obscured. The whole stump had lined up in long rows parallel to the line of pull of the tendon. The fibrous septums within the stump were broad and thick, and the blood vessels in the stump had increased in number. At the tip, the stump tapered off somewhat and became continuous with the tissues in the gap (fig. 2 *B* and *C*). The sheath tissues, especially about one side of the stump, were thick and passed over the end of the stump to help form the intervening tissue.

The intervening tissue or gap tissue was a broad, dense, fibrous band, which apparently came partly from the stump and partly from the sheath (fig. 2 *F*). As the middle of the gap was approached, the gap tissue became narrower, only to broaden out again when it neared the distal stump. Here it was again continuous, on the one hand with the end of the tendon, and on the other with the proliferated sheath of the distal stump.

The distal stump (fig. 2 *D* and *E*) was also proliferating, and was literally packed with nuclei. It fused imperceptibly with the intervening tissues with which the sheath also fused.

*FIFTEEN DAYS.*—*Dog S 21.*—An end-to-end suture was done with good apposition and without a great deal of tension. A cast was applied. Examination on the fifteenth day showed a separation of 2 cm. bridged across by fibrous-like tissue which transmitted the pull of the muscle. There was very slight adherence to the skin and fascia about the tendon.

Microscopic examination showed that the proximal stump was very nuclear throughout its whole length, and that its fibers were arranged in long rows parallel to the line of tendon pull. Toward its distal end, the stump began to taper off and to become continuous with the gap tissues. The silk had caused considerable commotion in the stump, and there was still a great deal of inflammatory reaction, and foreign body giant cells were not rare. The blood vessels were more plentiful than in normal tendon, and there was increase in the tissues about them. The normal fine connective tissue septums of the tendon were also wide and cellular. The sheath about the stump was thickened and dense, with its nuclei and fibers flattening out and lining up along the line of pull. These proliferated tissues passed distally over the end of the stump to fuse with the rest of the gap tissues, forming a tough fibrous strand.

The intervening tissues uniting the stump were made up of cells and fibers from the sheath, from peritendinous tissues and from the stumps. Toward the distal stump a silk suture and its knot had made a defect in the replacement tendon, and there was here a small area of inflammatory infiltration. The gap tissues, however, were securely fused to the stumps at each end.

The distal stump showed practically the same appearance as the proximal, i. e., proliferation of nuclei and fusion with the gap tissues.

*Dog S 32.*—The tendon was united nicely without undue tension, and a cast was applied to maintain relaxation.

The area was examined fifteen days later. The fascia and skin separated easily with a minimum of adherence. The tendon stumps had separated about 2 cm., but

were held together by a thick, fibrous strand, in which the silk suture was embedded. The whole region was covered by a glistening membrane, under which or through which the tendon moved. A pull of 28 pounds (12.7 Kg.) on the freed tendon broke the union at the tip of the proximal stump.

Microscopic examination was made of the distal stump only, which was seen to be very nuclear. Where the nuclei were thickest, the fibers were fewest. The fibrous septums in the tendon were wide and cellular. The sheath, while quite thick, did not appear to be very adherent to the tendon.

*EIGHTEEN DAYS.—Dog S 5.*—Both legs were operated on, and a tendon suture performed on both sides. No casts were used. Examination of the sites of suture was made eighteen days later.

On examination, it was seen that both stumps had separated about 4 cm., and that they were united by very thin strips, and the suture material was seen surrounded by red inflammatory tissue.

Microscopic examination showed about the same histologic picture in each stump. The proximal tendon end was bulbous, being covered by a thickened sheath which extended for a short distance beyond the stump before it broke up into loose strips of tissue. The fibrous septums were thickened and nuclear, the intratendinous vessels were increased in number, and there was perivascular infiltration or proliferation about them. At the end of the stump, the tendon had proliferated into the gap tissues, which were then made up of tissues from the sheath, the intratendinous connective tissue and the tendon proliferation. The distal stump had the same make-up as the proximal stump.

*Dog S 11.*—In this experiment a splicing suture with tension suture was performed. No cast was applied. Examination was made on the eighteenth post-operative day, and showed that there were few adhesions about the line of union which had separated about 2 cm. The area of suture was covered by a sheathlike membrane, firmly adherent to the region of suture, which did not permit gliding.

Microscopic examination showed that the gap was bridged across by a narrow strand of dense parallel tissue which appeared to have come from the mesotenon. The stumps, while very nuclear, had not produced enough tissue to bridge the gap, but had fused with the strand of dense tissue that united them.

*Dog S 20.*—A good approximation was obtained after division of the tendon and separation of it from its mesotenon for a distance of about 1.5 cm. on each stump. A plaster cast was applied.

Examination eighteen days later showed that the skin and fascia separated easily from the area of operation. However, the bulbous stumps and the thickened mass of tissue in the gap were firmly adherent to the underlying bone, allowing no motion whatever.

Microscopic examination showed that the ends of the stumps and sheath tissues projecting into the gap had become necrotic, owing probably to the fact that the mesotenon had been removed and that suture material under considerable tension had disrupted the tendon. The proximal end of the proximal stump was still viable and showed increase in number of nuclei as well as thickening of the fibrous septums. More distally, however, the tendon became quite thick; the tendon bundles, owing to cellular proliferation, became quite wide and spread out fanlike into the bulbous part of the tendon and then ended in a necrotic, inflammatory mass. The sheath tissues over the stump had proliferated somewhat and projected beyond the end of the stump, only to become involved in the necrotic, inflammatory mass that filled the gap.

The gap was filled with a thoroughly unoriented mass of granulation tissue.

The distal stump showed practically the same histologic picture as the proximal stump.

**TWENTY DAYS.—Dog S 19.**—An unsatisfactory end-to-end suture was made after separation of the proximal stump for 0.75 cm. from its mesotenon. Even with a great deal of tension, approximation to 0.75 cm. only was obtained. Examination twenty days after operation showed the skin and fascia freely separable from the line of suture. Adherence was present to other surrounding structures, however, since pull on the muscle failed to be transmitted.

Microscopic examination of the proximal stump showed a slight nuclear increase in its proximal end, with some thickening of the fibrous septums. The place through which the suture passed was quite bulbous, and about the silk was considerable infiltration with white blood cells and occasional giant cells. Distal to this bulbous area, the tendon narrowed down somewhat, and the nuclei were increased in number, though not to the extent they were in earlier specimens. Where suture material (knot) lay against the end of the tendon, the tendon fibers stopped abruptly; in other places the tendon passed imperceptibly into the gap tissues. The sheath and peritendinous tissues were thickened and had become oriented along the line of pull.

The gap had been securely bridged across along one side, mainly by the sheath and the peritendon tissue.

The distal stump was more nuclear than the proximal stump, and many mitoses were to be seen, especially in the region in which the stump passed imperceptibly into the gap tissues. The sheath tissues over the distal stump were also thickened and on one side were continuous with similar tissues from the proximal stump. Here they were dense, the nuclei being flattened and lined up in long rows along the line of tendon pull.

**TWENTY-ONE DAYS.—Dog S 3.**—A rather unsatisfactory suture with poor approximation was obtained on each leg. No cast was applied.

Examination three weeks after operation showed a separation of the stumps of 2 cm. on the right and 3 cm. on the left foreleg. The distal stump on the right side looked soft and necrotic, and a pull on the muscle above it was not transmitted. On the left side, however, some of the pull was transmitted, indicating that some function had been restored.

Microscopic examination (fig. 3) showed that there had not been the amount of separation of the stumps that the examination of the gross specimen suggested. The proximal stump was very nuclear throughout, though especially so at its tip, where numerous mitoses were seen (fig. 3 *D*). At its tip (fig. 3 *B* and *C*), it was not possible to determine just where the stump ended, since it blended imperceptibly with the gap tissues. The sheath over the proximal stump was thickened, and its nuclei and fibers were arranged in long rows parallel to the tendon pull.

The gap tissue was wide and looked tough and strong; most of it was a direct continuation of the stumps, only a small part apparently coming from the sheath. The whole of the gap was well supplied with blood vessels, most of which ran longitudinally.

The distal stump (fig. 3 *F* and *E*) looked a good deal like the proximal stump, and it, too, fused with the sheath tissues.

The histology of the tendon suture from the left leg was practically the same as that of the right leg.

**Dog S 4.**—This experiment presented the same histologic picture as the preceding one.

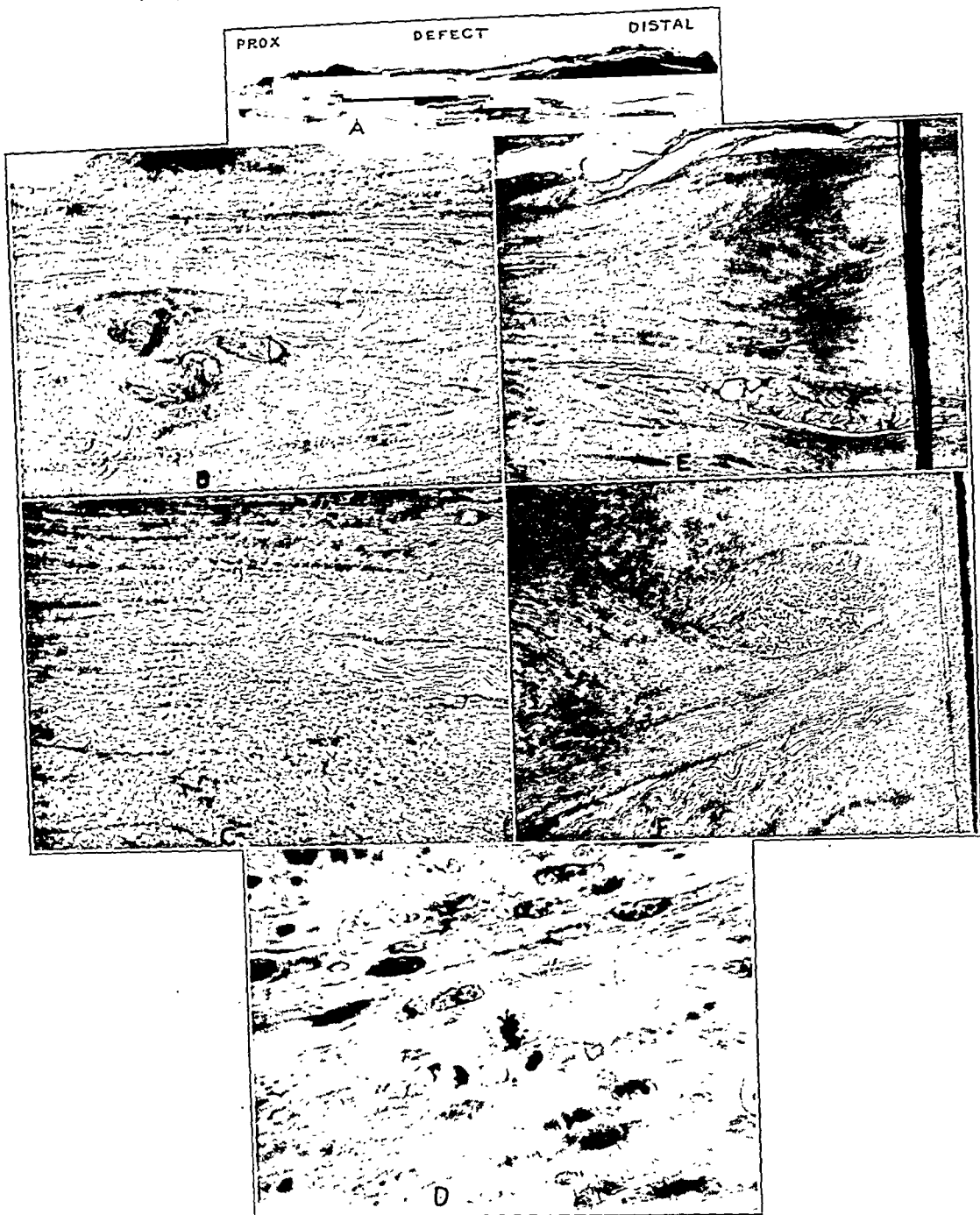


Fig. 3.—Sections through a three weeks old specimen S 3 (right leg). *A*, the entire specimen including proximal (*Prox.*) and distal stumps and intervening tissues. This shows that the proliferation from the two stumps has formed a central band of union between the stumps and that the sheath tissues have become more lax and are loosening up from the regenerating tendon. *B*, the end of the proximal stump, is highly nuclear and still shows evidence of active proliferation. It is continuous with the defect tissues, which cannot be distinguished from the tendon stumps. *E*, the end of the distal stump, is also continuous with the tissue in the gap. *C*, the end of the proximal stump, reduced from a magnification of  $\times 35$ . This photomicrograph was taken through the region at which it was thought the original stump ended. There is irregular but direct continuity of fibers. *F*, the end of the distal stump. This, as does the proximal stump, passes over directly into the intervening tissues. *D*, mitotic figure from the proximal stump.



**TWENTY-TWO DAYS.—Dog S 27.**—An end-to-end suture with slight tension was made, and a cast applied, which the dog wore for two weeks. After removal of the cast, the dog used the leg as freely as before operation.

Examination on the twenty-second postoperative day showed the tendon ends slightly bulbous, though they were well united and transmitted pull through the intervening tissues. The tendon broke through the middle of the bulbous portion of the proximal stump after a pull of 40 pounds (18.1 Kg.) was put on it.

Microscopic examination of cross-sections of the proximal stump showed increase in tendon nuclei and thickening of the fibrous septums. The gap was made up of a wide, thick strand of connective tissue well supplied with blood vessels.

**TWENTY-FOUR DAYS.—Dog S 10.**—A splicing suture was made in fairly satisfactory manner, except for the fact that one splicing segment was nearly torn loose from its mesotenon. No cast was applied.

The operative area was examined twenty-four days later. The skin and superficial fascia were not adherent to the region of suture; however, the tendon was apparently quite adherent to the sheath and the sheath securely attached to the bone, so that no motion was transmitted. The stumps had separated 3.4 cm., and were united by a thin, fibrous strand.

Microscopic examination showed the proximal stumps to be very nuclear, especially toward the tip, where no eosin-stained collagen fibers could be seen. This end went over gradually into the intervening tissues without any break. The sheath over the stump was quite thickened, well attached to the stump and had taken a longitudinally arranged structure parallel to the line of pull of the tendon. It passed over the end of the stump into the gap and took part in the formation of the intervening tissues. If, however, one traced the sheath farther distally, one found that it lost its dense fibrous structure and ended as loose disorganized connective tissue. The mesotenon under the proximal stump was very thick and vascular, and it too continued into the gap for a certain distance as a dense structure capable of withstanding tendon pull. The more proximal of the splicing bits of tendon was still alive and showed proliferative changes similar to those seen in the stump. It blended proximally and distally with the intervening tissues.

The distal stump had practically the same histologic appearance as the proximal. It would appear, then, that the gap between the two stumps had been so great that it could not be bridged without a graft.

**Dog S 13.**—A fairly satisfactory splicing suture was performed. Examination twenty-four days later showed few adhesions between the site of suture and the surrounding tissues. A sheathlike structure covered the newly formed tissue uniting the stumps, and the new tendon glided freely within it.

Microscopic examination showed that the splicing segments had remained alive and had bridged a gap of 1.5 cm. from stump to stump. The many mitoses and great nuclear increase in each stump were evidence that considerable tendon proliferation had taken place. The sheath was not so dense and fibrous as in previous sections, and was apparently taking over its gliding function.

**TWENTY-SIX DAYS.—Dog S 26.**—A satisfactory end-to-end suture was obtained, and a cast was applied. On examination, three and one-half weeks later, a nicely gliding tendon was found covered over by sheets of fascia. Test of strength was made of this tendon, which ruptured through the proximal stump with a pull of 16 pounds (7.3 Kg.).

Microscopic examination of the material showed that the whole of the stumps and intervening tissues were forming into a unified whole. The stumps were packed with nuclei, and the tendon fibers were not visible toward the tip, where

they went over imperceptibly into the gap tissues. The sheath, while thick, was not so thick as in earlier specimens. The suture material was still surrounded by inflammatory infiltration, but this was not so marked as it had been earlier. The gap tissue was being divided into longitudinal rows of nuclei and fibers and resembled tendon.

**TWENTY-EIGHT DAYS.**—*Dog S 25.*—A fairly satisfactory end-to-end suture was obtained, and a cast applied. The specimen was examined twenty-eight days after operation.

On gross examination, it was seen that the tendon glided freely beneath a rather thick, sheathlike tissue covering it. This sheath could be opened fairly easily, except for a few loose adhesions which bound it to the tendon. In an attempt to rupture the new tendon, a pull of 40 pounds (18.1 Kg.) was placed on it, which tore the muscle from the musculotendinous junction, but did not stretch or tear the tendon.

Microscopic examination showed that there was a separation of 1.5 cm. The proximal stump was more nuclear than normal tendon, and showed one particularly bulbous area a short distance proximal to its tip into which the tendon bundles passed, spread out fanlike and became exceedingly nuclear. Distal to this bulbous enlargement, the width of the tendon gradually decreased, until it blended or became continuous with the gap tissues. The nuclei in the stump were somewhat longer and more oval than in normal tendon and were lined up in longitudinal rows parallel to the line of pull of the tendon. The fibrous septums in the most proximal part of the stump were thickened. There was some increased vascularity of this stump.

The tissue intervening between the stumps looked like very nuclear tendon tissue. It was lined up in longitudinal bundles, was quite nuclear and moderately vascular and was continuous at either end with the stumps.

The distal stump, which was continuous with the intervening tissues, had practically the same histologic character as the proximal stump.

**THIRTY-FOUR DAYS.**—*Dog S 29.*—A fairly satisfactory end-to-end suture was obtained, and a cast applied. When examined thirty-four days later, the region of operation was seen to be moderately free from adhesions. The tendon was covered by sheathlike tissue, beneath which it glided freely. After the tendon was freed from all surrounding tissues, a pull of 36 pounds (16.3 Kg.) was insufficient to break through the line of union. Rupture did occur, however, at the musculotendinous junction.

Microscopically, there appeared to be an attempt at reformation of a synovial sheath. The stumps, while still exceedingly nuclear, were beginning to show a more definite alinement of the nuclei and fibers. They were directly continuous with the gap tissues, which were arranged in fibrous bundles as in normal tendon.

**THIRTY-SIX DAYS.**—*Dog S 30.*—A good end-to-end suture was obtained, and a cast applied. On examination five weeks later, a good functioning tendon was found which glided easily beneath a sheathlike structure. Both stumps were somewhat enlarged and bulbous; the proximal more so than the distal. When tested for strength, after removal of all associated tissues, the new tendon in the gap ruptured at 44 pounds (20 Kg.) of pull.

Microscopic examination was not satisfactory, owing to the disrupting effect of the test of strength. However, there was some suggestion that the synovial sheath was beginning to reform.

FORTY-ONE DAYS.—*Dog S 16*.—A fairly satisfactory splicing suture was obtained, and a cast applied. On examination forty-one days later, the two stumps were covered by a soft inflammatory mass of tissue, and there was no apparent union.

Microscopically, despite the gross appearance and evidence of considerable infection, the tendons had partially survived, and a union of a sort had been obtained through the soft inflammatory tissue. This union was a thin but dense fibrous strand in which the fibers and nuclei were lined up in parallel rows along the line of pull. The stumps, which were quite nuclear, passed over imperceptibly into this gap tissue.

#### THE PROCESS OF REPAIR IN A SUTURED TENDON

The examination of the gross as well as of the microscopic specimens of tendon sutures shows that there may be considerable variation between specimens. The variation is not only chronologic, but quantitative and qualitative as well, in that the rate of healing in some dogs may be quite rapid, while in others it may be slow; in some the amount of sheath proliferation may be excessive and so far overshadow the actual tendon cell proliferation that the latter appears unimportant. In some instances, the amount of inflammatory reaction may be so great as to make the suture a failure, or nearly so, while in others, the disposition of the silk within the tendon and the presence of knots between the ends of the tendon seriously interfere with healing. However, the process of healing appears to depend on the regenerative and proliferative powers of the two tissues entering into the formation of tendon. From this study it seems logical to assume that these two tissues (connective tissues and tendon tissue itself) have each a definite rôle or function to perform in the healing process.

During the first few days following suture, examination reveals a considerable amount of swelling and edema in the peritendinous tissues. The tendon stumps are swollen, have lost their natural mother-of-pearl sheen and appear pink or red instead of white. This coloration is due to the hyperemia within the tendon, as is evidenced by the fine longitudinal red striation, which can be seen if the tendon is magnified slightly. The stumps are practically always separated from 2 to 2.5 cm. (rarely more), depending on the type of suture and the adequacy of the immobilization. The suture may still be holding at this time, though it is rarely secure after the third day.

The defect between the stumps is filled by a red gelatinous exudate which can be easily scraped out, and which looks like granulation tissue. It has no tensile strength, does not hold the stumps together, and any function at this time must be due to the suture holding the stumps.

The sheath, which partakes in the general edema, is also thick and edematous, but in this early stage is either not adherent or very slightly adherent to the stumps and can be easily separated from the exudate.

Microscopic examination at the early stage of healing bears out the assumption that proliferative changes, while present in all the tissues, are not advanced far enough to afford functional union.

The stumps, always separated as just noted, end fairly abruptly against an early granulation tissue which lies in the defect. The tendon nuclei are swollen and fat and more round or oval than in normal resting tendon and appear slightly more numerous. Mitoses rarely appear before the fourth day. The intratendinous vessels are wide, and there is an increase in the cells about them. The fibrous septums of the tendon are thicker than normal, and at the ends of the tendon send cellular strands out into the granulation tissue over the tip. The silk suture is surrounded by white blood cells with an occasional giant cell. The distal stump shows the same changes as the proximal, though all through the experiments it has been noted that the proximal stump is always the more advanced.

The sheath tissues about the tendon are thickened and cellular. They have fallen into the gap over the end of the tendon and are taking part in the formation of the intervening tissues. Already, however, the tendon is quite vascular, and its fibers are arranged longitudinally with the line of pull of the tendon.

The defect between the two stumps is filled with an early granulation tissue. There are many red blood cells and fibrin, fibroblasts and leukocytes and beginnings of capillaries. As yet, the tissue is thoroughly disorganized.

About the end of the first week, a fairly definite structural continuity has been established by means of the sheath and peritendinous tissues. On gross examination, there is still seen a good deal of edema and redness, but this has not the same soft gelatinous consistency that was observed in the first few days. The defect between the stumps is now filled by a fusion of the sheath and peritendinous tissues with the organizing exudate to which the stumps are fused. The sheaths have also fused with the stumps, so that pull on the muscle above leads to movement of the whole mass of tissue. The stumps cannot now be separated without tearing up many adhesions. The suture material is usually deeply buried, though at times it is seen lying on the surface of the tendons.

Microscopic examination at this time (fig. 1) reveals a union of the stumps by a tissue proliferation from the sheath and peritendinous tissues. The stumps themselves, however, are beginning to proliferate and take part in the healing.

Both stumps are bulbous and are thicker than normal. This enlargement is due not alone to the presence of suture material, but to actual proliferative changes in the tendon itself. There is a great increase in the number of tendon nuclei. This increase, while especially

PROCESS OF TENDON REPAIR AS REVEALED BY  
EXPERIMENTS WITH TENDON GRAFTS

## TECHNIC OF EXPERIMENTS

To avoid the repetition of details of operative technic, which we do not desire to stress in this connection, a short résumé of the various types of operative procedure of grafts will be given here, and then only briefly referred to in the actual protocols of the experiments that follow.

In all experiments a segment was excised from the multiple tendon of the extensor carpi radialis. The gap thus left, which was practically always greater by 1 cm. than the length of tendon excised, owing to tonic retraction of the proximal stump, was replaced by a tendon graft taken from the same dog. In many instances this graft was taken from the corresponding tendon on the opposite leg; in other instances the original tendon tissue removed was put back into place to serve as a graft after it had been completely severed from its blood supply, while in still others a section of the extensor pollicis longus was excised and used as graft. In most instances, the graft was cut as long as the segment removed originally from the extensor carpi radialis. In a few cases, the graft was longer than the segment removed, but never as long as the resultant defect; i. e., in every instance the graft was sutured under tension. In a few of the earlier experiments, a careful closure of the divided sheath was made after the graft had been sutured in place; in the later experiments, however, sheath suture was not performed.

The suture material used was grade D twisted silk, lubricated with sterile petrolatum jelly. In the instances in which the sheath was closed after the graft was put into place 00000 china silk or 000 catgut was used to suture the sheath.

In dogs T 1 to 13, inclusive, the following method of suturing the graft in place was used. The stretch of tendon was excised, and a graft taken from the opposite leg. Through the center of this graft a strand of silk was run on a long number 11 beader's needle. This suture was then secured to the one stump by a lacing suture (Kanavel tendon suture), the silk again passed through the graft and secured in like manner to the opposite stump. One knot only was used. It was usually, though not in every case, possible to secure good apposition at the time of operation. In dogs T 14, 15 and 16 the gap was bridged across by overlapping the graft on the stumps. The graft was cut longer than necessary to fill the defect, and was laid across the ends of the stumps under tension, and the tendons sutured side-to-side at each end of the defect by through-and-through sutures.

In dogs T 17 and 18 and T 27 to 34, the ends of the stumps and graft were brought together by separate lacing sutures, i. e., the suture was passed back and forth in the tendon after the manner of the Kanavel suture, taking care not to leave any silk exposed. The knots were tied so as to lie between the ends of the tendon. In this manner, no silk lay in the central part of the graft.

In dogs T 19 to 26, the technic was the same as in T 1 to 13, except that the silk, instead of passing straight through the center of the graft tendon, was basted through the graft from end-to-end.

The sheath tissues were carefully sutured over the area operated on in dogs T 1 to 11, while in all remaining dogs no attempt was made to close the sheath. In all experiments, however, the sheath tissues around the graft were carefully preserved. In making the defect in the first eleven experiments, the sheath tissues about the excised tendon were also removed. In the rest of the experiments, however, the sheath was merely split longitudinally and the tendon alone excised. It

was found that in the instances in which the sheath was removed from the defect and in which the periosteum was exposed, very dense adhesions formed which held the graft securely to the bone.

Dogs T 1 to 16 were allowed free full use of the leg immediately after the operation. In dogs T 17 to 34, however, a plaster cast was applied for varying intervals to keep the radiocarpal joint in extension and the humero-ulnar joint in flexion.

#### PROTOCOLS OF EXPERIMENTS WITH TENDON GRAFTS

FOUR DAYS.—*Dog T 34.*—Transplantation of a 7 cm. piece of tendon plus peritenon was made into a 6 cm. defect of the extensor carpi radialis. A lacing suture was made through each end of graft and through each stump, with good apposition, and a plaster cast was used.

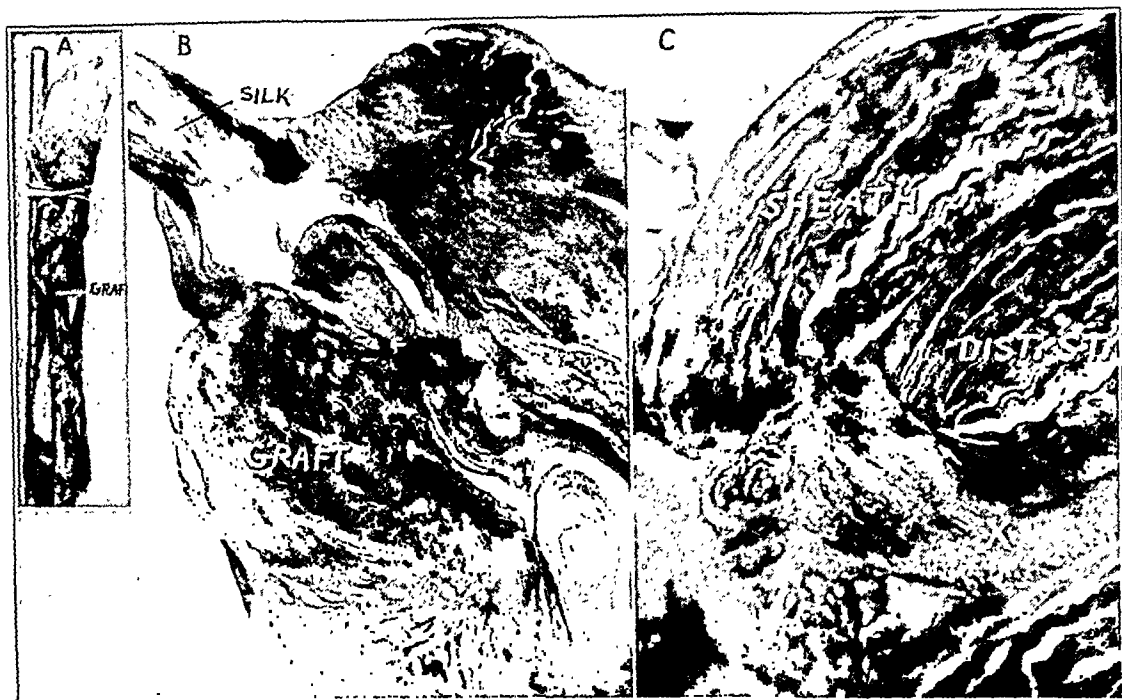


Fig. 4.—*A*, gross specimen of T 34 removed at the end of four days. *B*, photomicrograph of distal end of graft of T 34. *C*, photomicrograph of proximal end of distal stump, T 34; X stands for proliferating peritenonium internum.

The dog was killed at the end of four days. The skin and superficial fascia were separated fairly easily from the surface of the graft and stumps. The graft and stumps were swollen and edematous, red and granular in appearance. There was a 7 mm. separation at the distal suture line, still bridged across by the silk, but no separation at the proximal suture line. With traction on the muscle, the tendon pulled through the overlying tissues. A pull of  $4\frac{1}{2}$  pounds (2 Kg.) ruptured the tendon through the proximal stump just proximal to the suture line. The graft looked white, but did not rupture with the tension.

Microscopic examination of the distal suture line (fig. 4 *C*) showed that the proximal end of the distal stump was torn and disrupted by the suture, bundles of fibers were twisted about the silk, and there were some evidences of necrosis about these regions of trauma. Except for these areas, the stump was alive. The ten-

don bundles ran straight to the line of suture and then ended quite abruptly, as if cut off. The fibrillar character and wavy course of the tendon were maintained throughout. There were no evidences of nuclear proliferation in the stump. There was an increase in the cells about the intratendinous vessels, which were more prominent than in normal tendon. At the ends of the tendon there were V-shaped spaces between the bundles of fibers. These spaces were continuous with the intratendinous connective tissue (endotenonium) and also continuous with the granulation-like plug that covered over the end of the stump. The sheath about the stump was thickened and moderately infiltrated with leukocytes; it was continuous with the granulation tissue gap over the end of the stump, and was also proliferating over the silk suture that bridged the gap at this place.

The graft was largely viable and had about the same appearance as the distal stump (fig. 4 *B*). The silk here had caused a considerable disruption of the fibers,



Fig. 5.—Gross specimen of T 32 removed at the end of eight days. *A*, the tendon has not been separated from its bed. *B*, the tendon lifted from its bed. At *Gr.* the graft is shown.

but necrosis was very moderate. The intratendinous vessels were more prominent than normal, and there was an increase in cells about them. Most of the sheath tissues about the graft were alive, were moderately infiltrated with leukocytes and were somewhat thickened. No mitoses were seen in the tendon of the graft which ended rather abruptly alongside the silk suture. There was a thin layer of fibroblastic tissue which was pushing distalward along the sides of the silk suture, and which came apparently from the intratendinous connective tissue.

Microscopic examination was next made of the proximal suture line. It is difficult to determine just why rupture took place through the proximal stump. This stump was long, slim and narrow, but viable; its intratendinous vessels were prominent, and there was increase of cells about them. The area through which rupture took place was frayed and torn, and there was some loss of nuclei here, which might indicate an area of necrosis. In places, the tendon fibers were sepa-

rated by accumulations of red blood cells. The sheath tissues about the proximal stump were very thin, and when traced toward the graft looked as if the parts had been torn away.

*Dog T 21.*—Lacing sutures were made into each stump, and graft threaded over the silk between the stumps. A cast was applied. The dog died four days after operation. At postmortem examination, no separation was found at the proximal suture line, but about 5 mm. separation at the distal suture line, which was bridged across by the silk. The proximal stump and graft were gray. The whole area of operation showed a moderate amount of bloody exudate.

Cross-sections showed the distal stump surrounded by a rather thick and somewhat edematous sheath from which in several places cellular septums passed into the substance of the tendon. The tendon was not changed much in appearance from normal tendon, although in the areas around the fibrous septums the cell content was increased. This cellular increase was due both to an increased number of cells about the blood vessels and to an increase in the number of tendon cells among which occasional mitoses were seen. The flat type of tendon nucleus predominated, except in the region of the vascular endotenonium, in which the nuclei were becoming fatter and more vesicular. The sheath was somewhat edematous, and showed an area of white cell infiltration and also an area of fibroblastic proliferation.

SEVEN DAYS.—*Dog T 24.*—Transplantation of a 3 cm. graft plus paratenon was made into a defect in the extensor carpi radials. The graft ruffled up when tension was applied. A cast was applied.

The animal was killed at the end of seven days. The skin and superficial fascia were easily separated from the underlying graft and stumps. There was, however, adhesion between the tendon and the deep fascia of the foreleg. There was no separation detectable on macroscopic examination. Pull on the muscle resulted in about 60 degrees of motion at the radiocarpal joint.

On examination of the microscopic specimen with the naked eye (fig. 25), it was possible to distinguish the three areas, the graft and the two stumps. The proximal suture line was very narrow; not over 5 mm., while at the distal suture line there had been some overriding of the tendons, and there was no straight line of apposition. The proximal stump presented a fairly normal appearance (fig. 7 B); the tendon fibers were wavy in their course, and there was no suggestion of increase in nuclei until the suture line was approached. There was, however, considerable increase in cells about the vessels lying in the tendon. As the suture line was approached, this perivascular proliferation was seen to push outward into the tissue uniting graft and stump (fig. 6 A). At the suture line, the tendon was very nuclear and sent feather-like prolongations into the uniting tissue. In places, the intermixture of tissues was so far advanced that one could not distinguish between the elements derived from tendon, those derived from proliferation of cells about the intratendinous vessels and those coming from the sheath and other tissues that had pushed into the defect. Numerous mitoses were seen in the zone of tendon proliferation (fig. 7 C). The silk had produced defects in the stump; these were filled with an organizing granulation tissue that contained a few giant cells.

The sheath about the stump was thick and proliferated (fig. 6 C). It was infiltrated with leukocytes, but was beginning to line up in long parallel rows of fibers which ran across the gap tissues to become continuous with sheath tissues of the graft. As the sheath crossed the gap, it sent cellular and fibrous bundles (fig. 6 A) into it, which intermingled with the tissue here, while some united with the end of the graft.



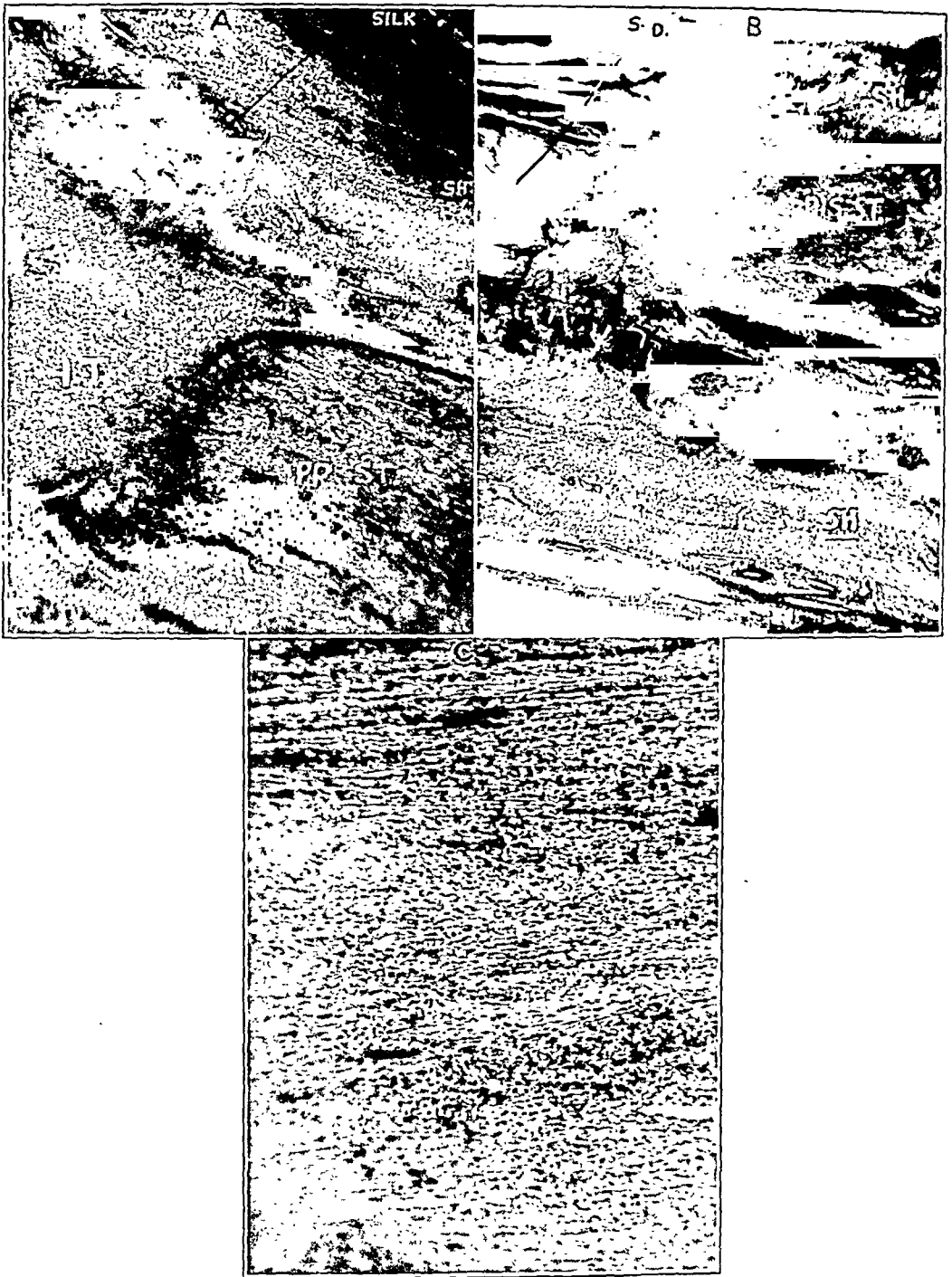


Fig. 6.—Photomicrographs of tissue from T 24 removed seven days after operation. *A*, the distal end of the proximal stump (*Pr. St.*) ends against the intervening tissue (*I. T.*) in a hazy, deeply eosin-stained, irregular edge in which mitoses are seen with higher magnification (fig. 7 *C*, *Mit.*). The sheath (*Sh.*) is thick and proliferated. *B*, the proximal end of the distal stump (*Dis. St.*) surrounded on all sides by the thick proliferated sheath (*Sh.*) ends against a rather large defect, due to the silk suture. *S. D.* stands for silk defect. *C*, the sheath over the stumps and graft is very cellular, but shows definite longitudinal arrangement of its fibers.

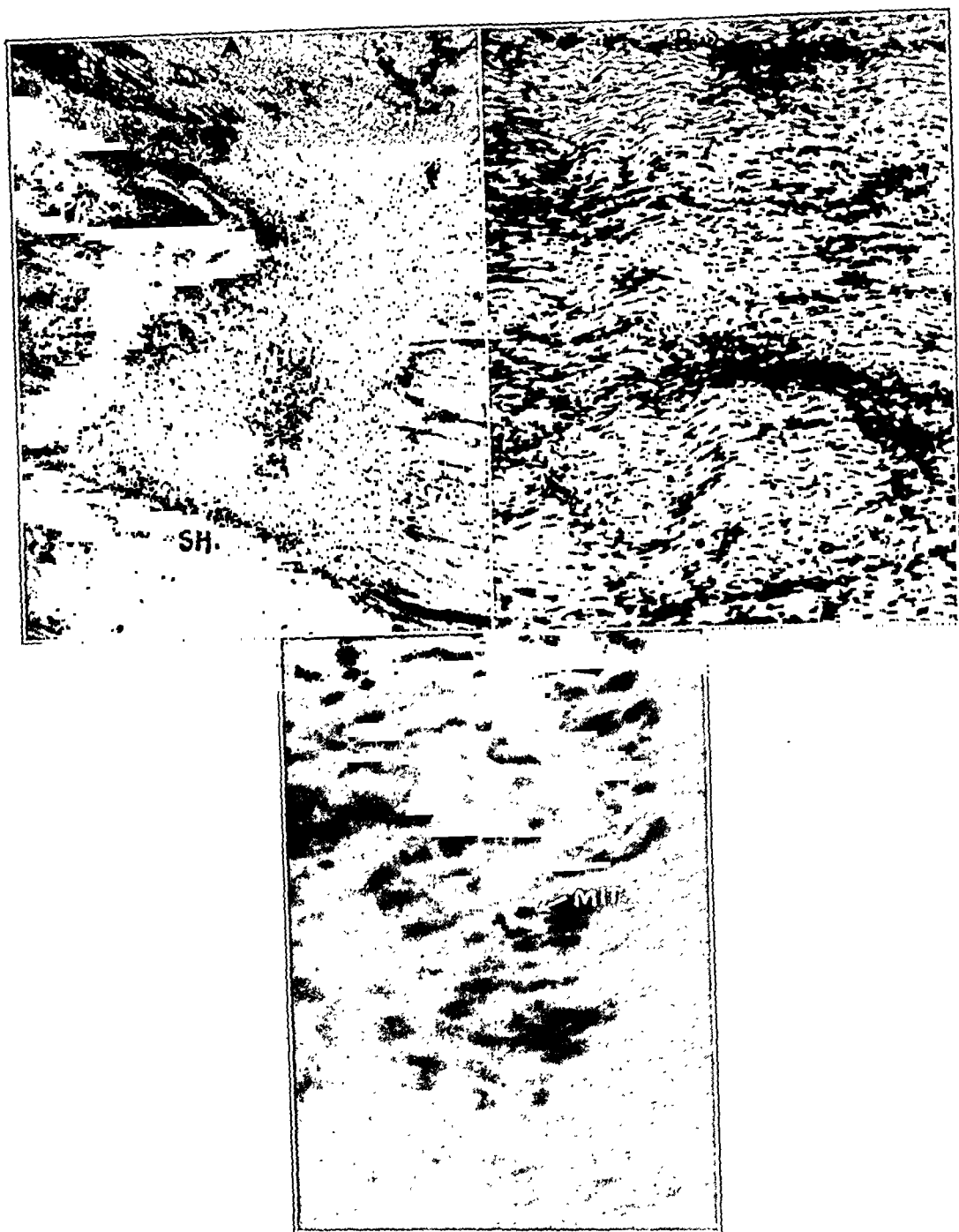


Fig. 7.—Photomicrographs of tissue from T 24 removed seven days after operation. *A*, the proximal suture line shows a small gap between the proximal stump (*Pr. St.*) and the graft (*Gr.*) filled up with a fairly dense intervening tissue (*Int. T.*), while to either side the gap is bridged across by proliferated sheath tissue. *B*, the proximal stump under slightly higher magnification shows the increased number of blood vessels (*B. V.*) and a great increase in number of tendon cells. *C*, higher magnification showing the changes in size and shape of the tendon cells with occasional mitoses (*Mit.*).

The gap tissues (fig. 7 *A*) were beginning to line up in rows parallel to the course of the tendon pull. There were some areas in which giant cells and small round cells appeared to have accumulated around bits of silk.

The graft (fig. 8 *A* and *B*) was readily recognizable as tendon, though it was rather badly broken up by the suture material. At the proximal suture line, it showed a blue cellular zone in which mitoses could be found. It was more vascular than normal at the suture line (fig. 7 *A*), and there was a considerable increase of cells about these parallel vessels. Where the vessels came to an end at the suture line, long rows of fibroblasts and connective tissue cells radiated into the intervening tissues. The nuclear end of the tendon had lost its wavy fibrillar

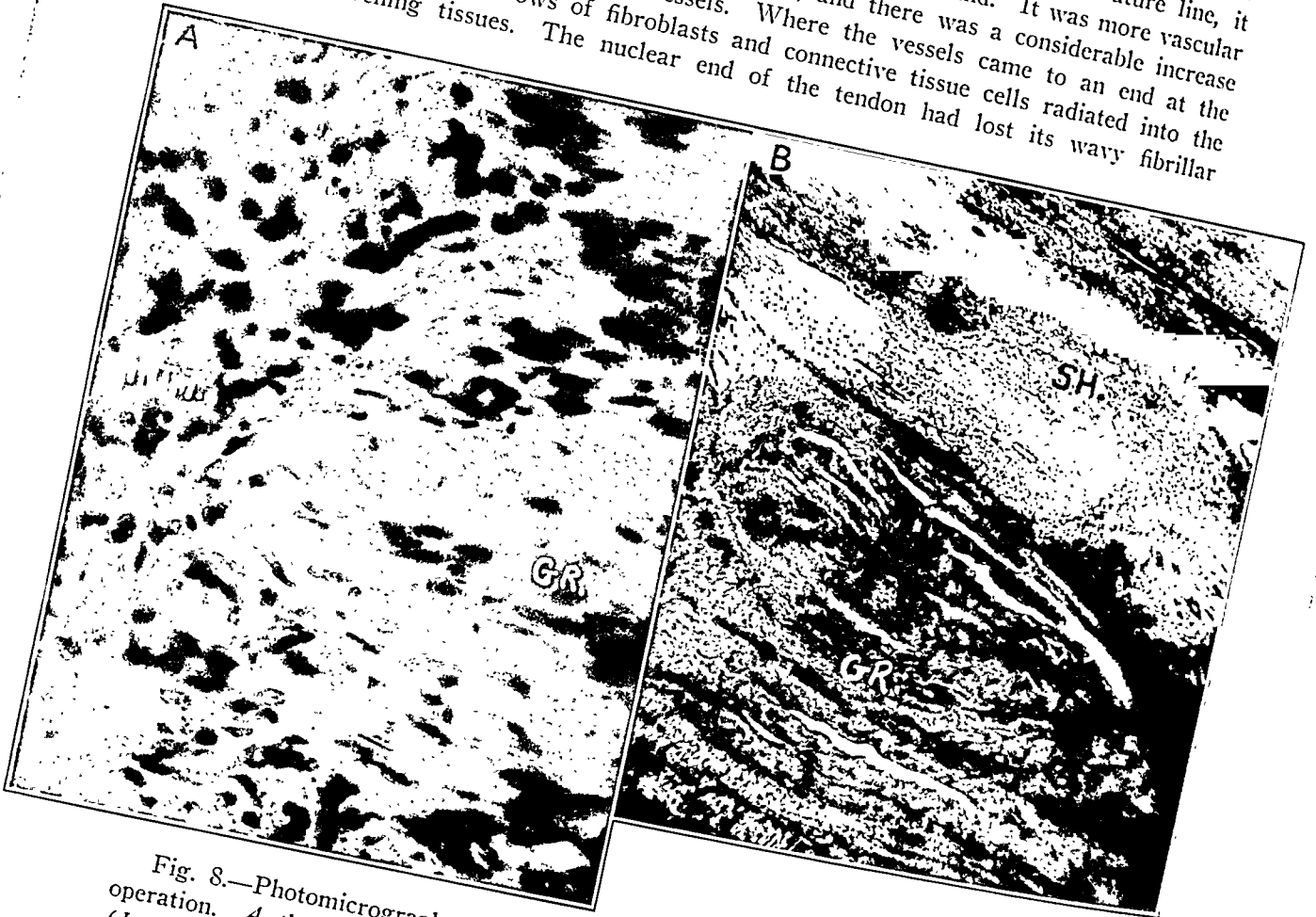


Fig. 8.—Photomicrographs of the graft removed from T 24 seven days after operation. *A*, the proximal end of the graft where it abuts the intervening tissues (*Int. T.*). The changes in size and shape and the increase in the number of the nuclei are well shown. *B*, central part of the graft showing the thick proliferated sheath (*Sh.*) and the nuclear increase in the graft.

appearance; the tissues about the nuclei took the stain more evenly, though one could usually detect a longitudinal arrangement in them. From the end of the graft, feather-like cords of cells pushed outward to become intermixed with the intervening tissues (fig. 8 *A*). Mitoses were to be seen in the end of the graft. The central parts of the graft, especially toward its distal end, showed areas of necrosis, but these were not of great extent. The silk had produced defects which were being healed by organizing granulation tissue. At the distal end, the graft and stump overlapped somewhat. About one half of the distal end of the graft

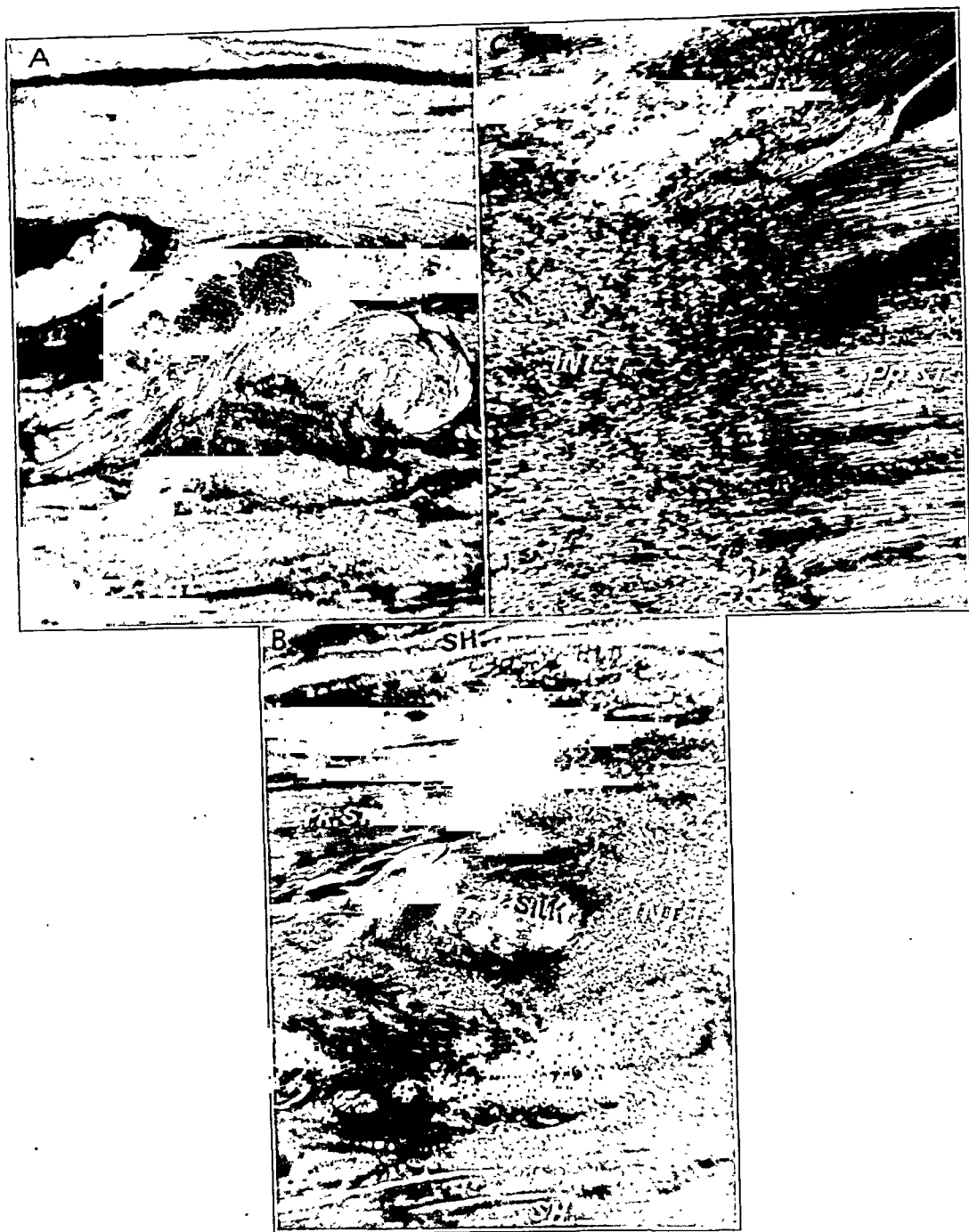


Fig. 9.—Photomicrographs of specimens removed ten days after operation. *A*, the proximal stump of T 5 which shows the destruction caused by the suture material and the increase in tendon nuclei with the straightening of the fibers. *B*, the distal end of the proximal stump (*Pr. St.*) of T 17 ends in a dark blue zone against the intervening tissue (*Int. T.*). The presence of a bit of silk here deflects the proliferating tendon to either side. The sheath (*Sh.*) is seen to be continuous over the defect. *C*, under slightly higher magnification, the hazy end of the proximal stump (*Pr. St.*) of T 17 shows penetration of the proliferating tendon into the intervening tissues (*Int. T.*). The cellular increase about the intra-tendinous vessels is also well shown.

was necrotic. The other half of the graft was viable and contained many longitudinal blood vessels, but there was not the nuclear increase such as was found in the proximal end of the graft. The sheath about the graft was thick, long strands of connective tissue fibers were forming in it, and it was infiltrated with leukocytes. The sheath was directly continuous with the sheath over the proximal and distal stumps.

The distal stump was badly broken up by the suture about which were leukocytes and occasional giant cells. The tip of the stump showed some increase in cells, but not so much as was seen in the proximal stump.

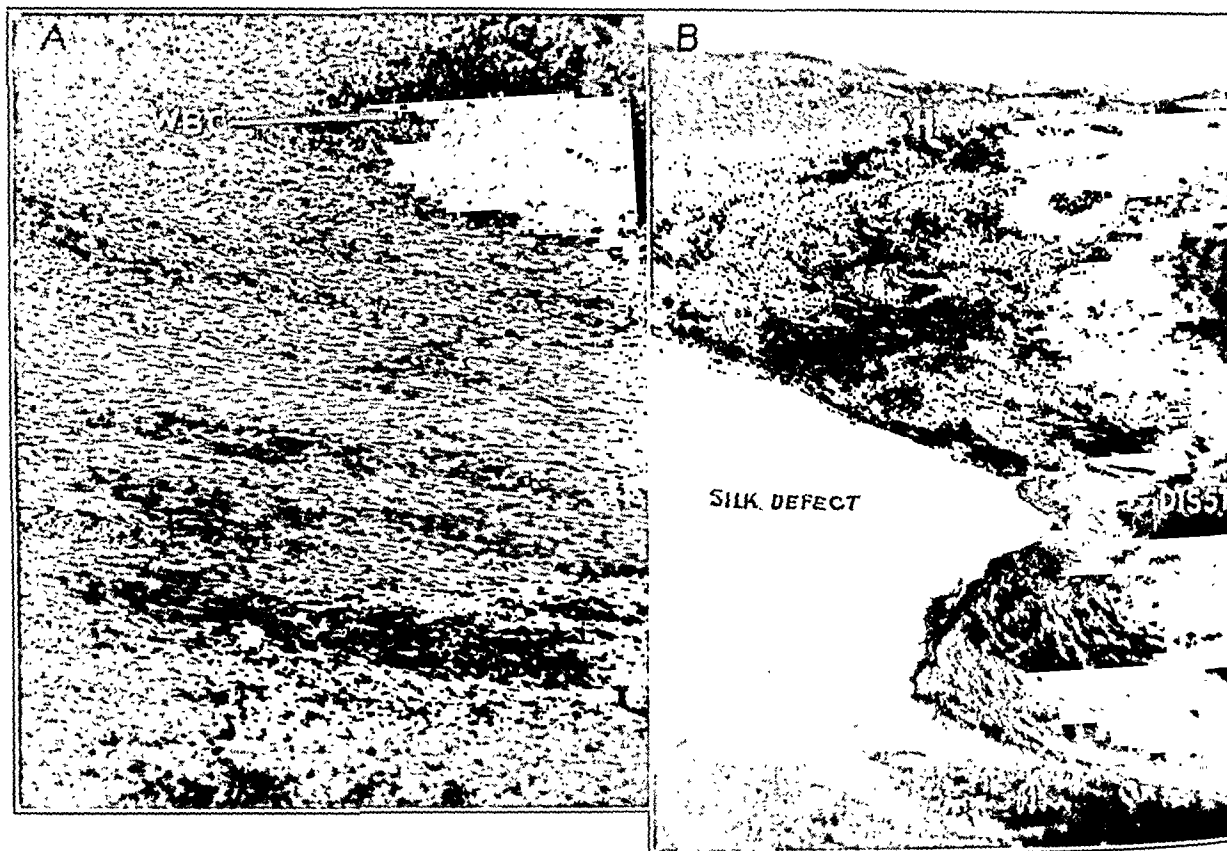


Fig. 10.—Photomicrographs of specimens removed ten days after operation. *A*, the sheath over the distal stump of T 5 is becoming well organized into strong fibrous tissue lined up in horizontal bands parallel to the line of pull. Occasional accumulations of white blood cells are seen. *B*, the distal stump of T 17 (*Dis. St.*) ends abruptly against a defect due to the silk suture. This defect is efficiently bridged across by proliferated sheath (*Sh.*).

*Dog T 14.*—Transplantation of a 2 cm. graft, taken with its sheath from one extensor carpi radialis, was made into a defect left by removal of 1 cm. from the opposite tendon. The graft was threaded over a double strand of grade D silk and then secured to the stumps by side-to-side suture. The sheath was not sutured, and no cast was applied.

The animal was killed seven days after the operation and the leg examined. There was no union. The graft had entirely disappeared, and the tendon suture

lay in the proximal stump. There were many adhesions about the area in which operation had been performed. The space between the stumps was filled with gelatinous material. The microscopic specimen was lost.

**EIGHT DAYS.—Dog T 15.**—Transplantation of a 2.25 cm. graft plus its sheath was made into a defect left by removal of 1 cm. from the extensor carpi radialis. No cast was applied.

The animal was killed on the eighth postoperative day. The suture lay free between the separated stumps, the gap being filled with a gelatinous material containing small bits of necrotic tendon, evidently the graft.

Longitudinal sections through the proximal stump and the proximal one half of the intervening tissues showed that the gelatinous material referred to was becoming slowly organized (fig. 11 C). The peritenonium internum and externum of the proximal stump and the connective tissue in and about the muscle attached to the stump were thickened and contained numerous large blood vessels. On low power microscopic examination, the connective tissues about and in the tendon and muscle were seen to run directly and continuously into the intervening tissues. Also, strands from the end of the stump were pushing distally into the intervening tissue. Some red, eosin-stained areas in the intervening tissues suggested remnants of the graft.

The cellular increase in the stump was quite apparent under higher magnification. The increase was most marked at the end of the stump and became less and less apparent as the proximal part of the stump was approached. From the end of the stump, delicate, feather-like strands of tendon cells could be seen to push distally into the intervening tissues, where they could be distinctly traced for some distance. The nuclei in the tendon at its growing tip were much increased in number and were more oval and not quite so darkly stained as in the enlarged tendon more proximally, and mitoses were to be seen among them.

There was marked increase in the amount of the perivascular tissues within the tendon. The strips of connective tissue, ordinarily narrow and thin, were broad and thick; they were made up of fibroblasts, some few white cells and numerous oval cells with vesicular, well staining nuclei, which were thought to be endothelial cells.

The connective tissues between the muscle and tendon were also thick and proliferated. Although very much infiltrated with white cells, the main substance was made up of long strands of young connective tissue and fibroblasts. These strands along with those from the endotenonium internum pushed distally into the intervening tissues, and with the proliferation from the end of the tendon were serving to establish continuity.

The intervening tissue (fig. 11 C) was an organizing granulation tissue which was being invaded by strands from two sources. Proximally, there came strands from the proximal stump and from the connective tissues in and about the stump. From the distal end was another source of connective tissue and tendon, i. e., from the graft and its sheath structures. There were two areas of massive leukocytic infiltration which were being slowly organized. About these areas, however, and through them passed fibroblastic and tenoblastic strands, which were making for continuity.

The graft (fig. 12 D) was recognizable as a remnant of tendon tissue which was blending in with the tissues surrounding it. From its ends long delicate fibrils and many nuclei were pushing proximally and distally to become lost in the fibrous and fibroblastic tissues that served to effect union. Mitoses were not seen in the graft itself nor in the fibrils, but from the large vesicular character of the

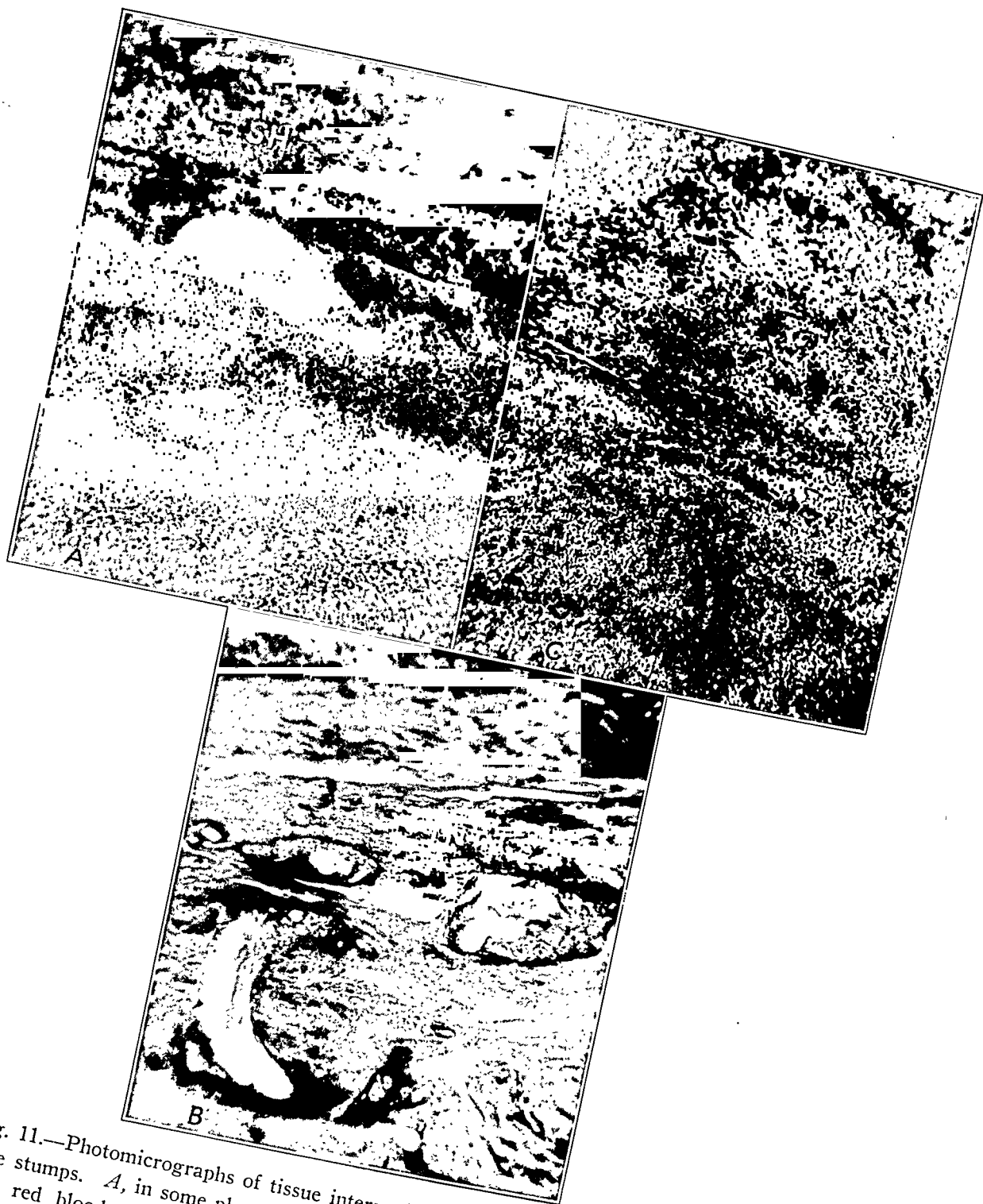


Fig. 11.—Photomicrographs of tissue intervening between the ends of the grafts and the stumps. *A*, in some places in T 5 the central area is merely an accumulation of red blood cells becoming infiltrated with white cells. In some places organization is beginning. The sheath (*Sh.*) from stumps and graft have bridged the defect. *B* (T 17, ten day specimen), the silk knot interferes with the organization of the intervening tissue (*Int. T.*), but the proliferated sheath helps to maintain union until organization is complete. *C* (T 15, eight day specimen), the organization of the intervening tissues takes place by the ingrowth of vessels and fibroblasts as well as by the ingrowth of tenoblasts.

nuclei and their great increase in number it must be assumed that the tendon cells had multiplied. There was considerable infiltration of this area with white blood cells.

The sheath tissues had been removed along one side of the graft. On the opposite side they were thickened, and the synovial lining was absent. Numerous blood vessels were present.

Microscopic examination of the distal stump revealed marked changes. There was great increase in the number of intratendinous vessels and of the cells of the peritenonium internum which stood out as thick cellular strips, breaking up the longitudinal arrangement of the tendon fibers. The sheath along one side of the tendon was quite vascular, moderately thick and made up of longitudinal strands of connective tissue. Study of the tendon showed numerous areas of degeneration through it, often fairly extensive necrosis, with white blood cell infiltration and replacement by proliferation from the cells of the peritenonium internum. Only in spots did one see any evidence of tenoblastic proliferation.

It was evident that the distal stump not subjected to pull was slowly degenerating and being replaced by scar tissue mainly of connective tissue origin.

*Dog T 32* (fig. 5).—Transplantation of a 2.5 cm. graft into a defect of similar size in the extensor carpi radialis tendon was made and a cast was applied.

The dog was killed on the eighth day. The skin and superficial fascia were quite easily separated from over the graft area. Pull on the muscle above showed that the tendon was sufficiently united to extend the joint. There had been a 1 cm. separation at the distal suture line, but the ends were still held together by the suture. This pulled out, however, when a pull of 4 pounds (1.8 Kg.) was applied.

The microscopic section consisted of the proximal stump and a small bit of the graft still attached to it. The stump was recognizable as normal tendon in which few changes had taken place. It was covered on either side by a very dense sheath which included also the remaining bit of graft. Very few changes from the normal were apparent in the proximal stump, except in its distal end, where there was some nuclear increase and a proliferation of fibers from it which could be traced into the intervening tissues.

The sheath tissues were quite thick and vascular. Well developed, longitudinally arranged fibrous tracts ran through it.

The graft appeared viable, but no signs of cellular proliferation could be made out. (The sections were poor.)

**NINE DAYS.**—*Dog T 30.*—Transplantation of a 2 cm. graft of tendon plus its paratenon was made into a defect of similar size in the extensor carpi radialis. A very small and slender tendon was used as graft, and a cast was applied.

The animal was killed on the ninth postoperative day. The dog had died several hours before the tissues were fixed. There had been a 2.5 cm. separation at the proximal suture line, and the graft which lay near the distal stump looked soft and gray. Sections of tissue were removed from the stumps and graft for cross-sectioning.

Microscopic examination of the proximal stump showed some increase in the intratendinous connective tissue; otherwise, in the section studied (a cross-section) no notable changes were found.

Cross-sections of the graft showed most of it to be alive, with only here and there spots of degeneration. Certain peculiar areas containing giant cells were found, and were assumed to be degenerating bits of striated muscle included in the graft. We could make out no evidence of tendon cell proliferation. The sheath



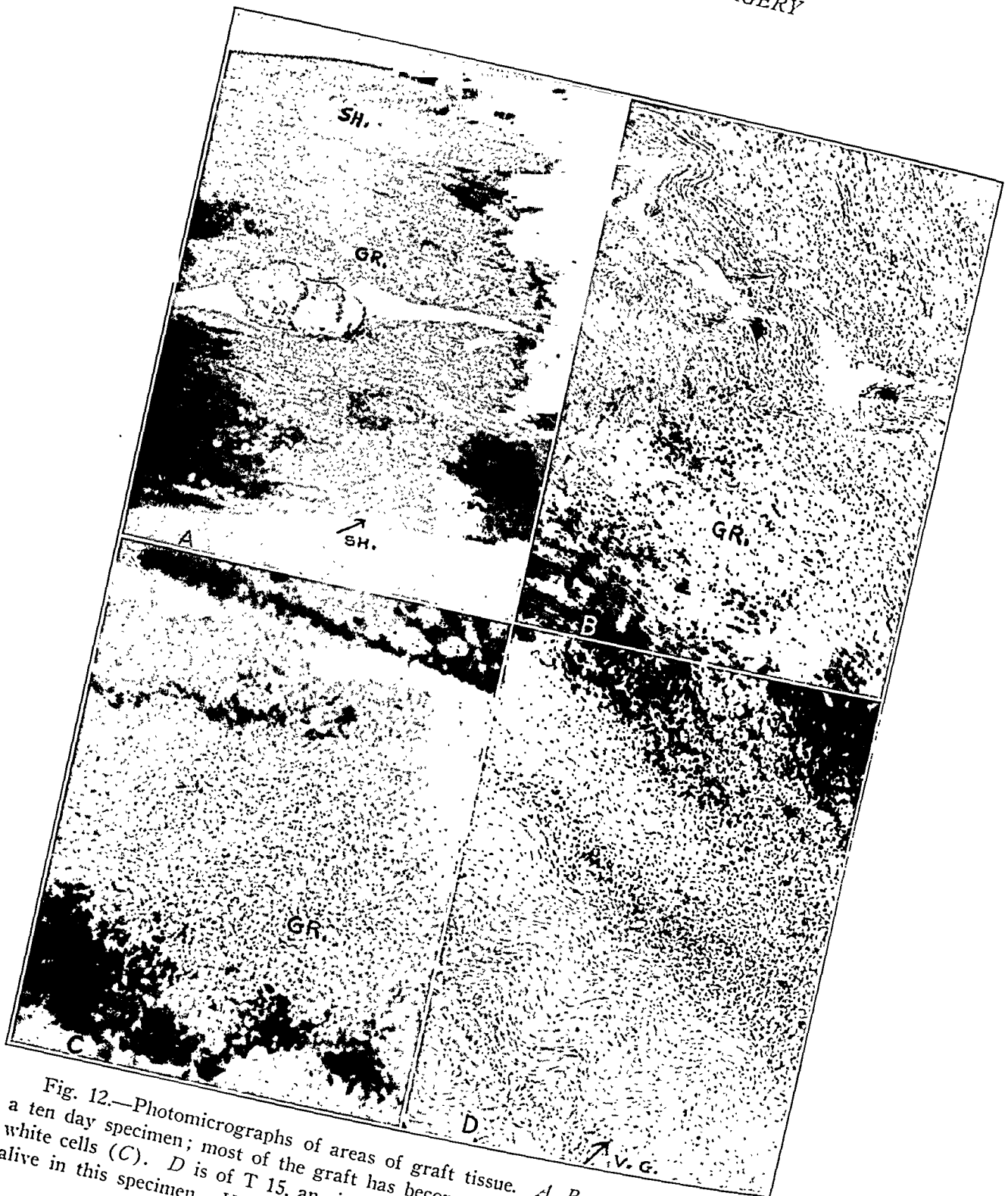


Fig. 12.—Photomicrographs of areas of graft tissue. *A*, *B* and *C* are of T 5, a ten day specimen; most of the graft has become necrotic and is infiltrated with white cells (*C*). *D* is of T 15, an eight day specimen; parts of the graft are still alive in this specimen. *V. G.* stands for viable graft.

tissues about the graft were thickened and quite vascular. There was no evidence of a synovial membrane about the tendon.

The tissue intervening between the graft and the distal stump contained a bit of silk about which there was inflammatory infiltration, and to either side of which (more marked along one side than along the other) was a band of quite nuclear and vascular dense connective tissue.

The distal stump had been very much broken up by the sectioning and showed merely a strand of silk contained in tendon tissue. These sections were very poor and were not of much value.

TEN DAYS.—*Dog T 5*.—Transplantation of a graft of tendon plus its sheath-tissue about 2.5 cm. long was made into a defect of the same length in the tendon of the extensor carpi radialis. Lacing sutures were placed in each stump, and the graft was threaded over a suture passing from stump to stump.

The tendon was removed on the tenth postoperative day. The whole mass formed a continuous, though rather bulky looking, tendon.

The microscopic specimen consisted of a longitudinal section of the replacement tendon, which was made up of the two stumps of the extensor carpi radialis bound together by a definite band of tissue which contained the graft. The graft itself lay much nearer to the distal than to the proximal stump.

The proximal stump (fig. 9 A) had been rather badly broken up by the suture material about which there was considerable round cell infiltration. Giant cells were seen occasionally among the round cells, but they formed no prominent part of the picture. The vessels and intratendinous connective tissue of the tendon were both increased throughout. The tendon tissue itself showed little change in its proximal part at the musculotendinous junction. More distally, however, the changes were striking. The tissue became much more cellular and was broken up by longitudinally running strips of dark blue-stained cellular tissue. Some of these strips were areas of cellular proliferation about the intratendinous vessels; others, however, appeared to have no relationship to the blood vessels, but had developed from the tendon itself. Study of the tendon through the distal part showed its nuclei to be fatter and more oval. The nuclei were increased in number, and mitoses were seen. As the end of the tendon was approached, the cells became more numerous, and the deep eosin-staining character of the collagenous material became less apparent. Mitoses were more frequent, and the tenoblasts appeared to push outward into the intervening tissue, where they became lost among the other cellular elements.

The sheath over the proximal stump was dense, thick and vascular. It pushed distally over either side of the stump and could be traced more or less continuously to merge indistinguishably with the sheath tissues about the graft.

In the region between the proximal stump and the graft the intervening tissues were represented by an outer layer of dense connective tissue which was traced from the sheath of the proximal stump to the sheath of graft (and incidentally to the sheath of the distal stump) and a central cellular reactive zone. In this zone were numerous leukocytes, red blood cells, fibroblasts and here and there long strands of connective tissue. This was a granulation tissue which was becoming organized. Security of union was due, however, to the outer layer of sheath proliferation.

A good deal of the graft (fig. 12 A, B and C) had disappeared or was necrotic and infiltrated with leukocytes; and a good deal of the tissue about it was organizing granulation tissue. However, its sheath tissues along one side (fig. 12 A) were thick and proliferated and were in direct continuity with similar tissues proceeding from (or at least in direct continuity with) sheath tissues of the two

stumps. Parts of the grafted tendon were still alive, and here were found the same evidences of tendon proliferation that were found in the proximal stump, i. e., increase in number of nuclei, increase in size of nuclei with assumption of a more oval and vesicular type of nucleus, mitoses, decrease in eosin-staining substance and tenoblastic proliferation into the intervening tissues.

Between the distal stump and graft was granulation-like tissue, presumably reaction about the silk suture (fig. 11 *A*), while on one side was a layer of connective tissue which afforded the effective union.

The tendon of the distal stump showed the same changes that were described in the proximal stump, i. e., increase in blood vessels, increase in intratendinous connective tissue and increase in sheath tissue. At its most distal end the stump had the appearance of normal tendon. More proximally, however, where it abutted the intervening tissue and for some little distance distal to this line, there were bands or zones running through it that showed cellular increases. Mitoses were seen scattered through the distal stump also, more numerous some little distance from the suture line itself, since right at the suture line there was some tendon necrosis.

*Dog T 17.*—Transplantation of a 1 cm. tendon graft was made into a 1 cm. defect of the extensor carpi radialis, and a cast was applied.

The animal was killed on the tenth postoperative day. The graft was seen to lie between the two stumps, united to them at either end by a gelatinous-like, soft-looking material which preserved the continuity of the replacement tendon (fig. 25).

From gross examination of the specimen one would suspect that the preceding sections of T 5 would be altogether different from those of T 17. As a matter of fact, there were the same histologic findings. Union was due to the sheath bridging over the defect (figs. 10 *B* and 8 *B*), while both stumps (fig. 9 *B* and *C*) were beginning to send tenoblastic fibrils into the intervening tissues. This soft gelatinous intervening tissue was microscopically the same as the more fibrous-looking tissue from the preceding specimen. More of the graft was viable than in T 5; there were here signs of proliferation, which were less marked than in the stumps. The reaction about the silk and the knots lying at the end of the graft formed some impediment to the penetration of these tissues by tenoblasts from the graft.

*Dog T 33.*—Transplantation of a very long segment of a small narrow tendon with its peritendinous tissues was made into a defect in the extensor carpi radialis tendon. A plaster cast was applied.

The animal was killed on the tenth postoperative day. The graft was found to have pulled away entirely at the distal suture line.

Most of the graft was alive and had preserved in many places the wavy course of its tendon fibers. Union between the proximal stump and the graft was due to the proliferated sheath. Histologic findings were the same as those for dogs T 5 and T 17.

**ELEVEN DAYS.**—*Dog T 4.*—Transplantation of a graft of tendon plus its sheath about 2.5 cm. long was made into a defect of the same length in the extensor carpi radialis. The graft was threaded over a double suture of grade D twisted silk, which was fastened by a lacing suture into each stump. The dog was killed on the eleventh postoperative day. The regenerating tendon was considerably longer than the original tendon, but it was continuous.

Microscopic examination on the eleventh postoperative day showed about the same picture as did the specimens previously described for the tenth postoperative

day. The two stumps were found to be separated by a considerable gap, the central part of which contained the silk, with organizing granulation tissue about it. To either side were strands of connective tissue which could be traced fairly satisfactorily from stump to stump and included the sheath tissue of the graft.

The stump showed more evidences of proliferation than were found in the preceding sections. There were large areas of tendon in which the nuclei were greatly increased in number, large, oval, pale and vesicular, throughout which mitoses were liberally scattered. These areas of proliferation occurred not only close to, but also at quite a distance from, the suture line. At the distal end of the proximal stump, tenoblastic fibrils were seen running outward to mingle with the granulation tissue.

Although about one half of the graft seemed to have disappeared, the rest of it was quite vascular. The parts that were alive showed tenoblastic proliferation.

Here, as in specimens at the tenth day, the stump and graft were taking active part in the regenerative process. Union, however, was due to sheath tissues.

**TWELVE DAYS.—Dog T 23.**—Transplantation of a 1.5 cm. tendon graft plus its peritendinous tissues was made into a defect left by removing 1 cm. from the extensor carpi radialis. The graft was threaded over two sutures, which were fastened by a lacing suture into the proximal and distal stumps. A cast was applied.

The animal was killed on the twelfth postoperative day. The stumps and the graft were found to have fused into a solid mass (fig. 25) which was adherent to the deep fascia. The union looked very strong, but its tensile strength was not tested.

Microscopic examination showed that the stumps and graft were united into a definite structure, in the formation of which the tendon tissue itself was beginning to play a quite definite rôle.

The stumps (fig. 13 *B* and *C*) were quite vascular; the vessels for the most part ran longitudinally through them, and divided them into longitudinal strands. There was considerable increase in the cells about these vessels. The proximal stump and, to a lesser extent, the distal stump, were more nuclear than normal through the whole extent, though more so where they abutted the intervening tissues. This nuclear increase was not general or uniform, but tended to occur in zones and strips. Where the end of the stump lay against the intervening tissues, the tendon had a feather-like edge from which fine fibrillar strips of tenoblasts projected into the granulation tissue, where they became lost. Mitoses were to be seen in the tendon throughout the very cellular areas.

The graft (fig. 16 *B* and *C*) showed changes identical with those found in the stumps. It was well vascularized and very little of it appeared to have become necrotic. Most of it had been converted into a cellular proliferating tendon, with, here and there, stretches of red, deeply eosin-stained, unchanged tendon. From either end, fibril-like strands of tenoblasts (fig. 16 *C*) were pushing outward toward the stumps and taking part in the organization of the intervening scar tissue.

The silk lying between stumps and graft was being healed into place by a definite organization of the granulation tissue about it. The fibers and cells in this granulation tissue were beginning to line up in long rows or strips parallel to the line of pull of the tendon.

The sheath tissues from graft and stumps (fig. 15 *A*) were seen to bridge across the defect areas and were made up of dense, longitudinally arranged bands of connective tissue.

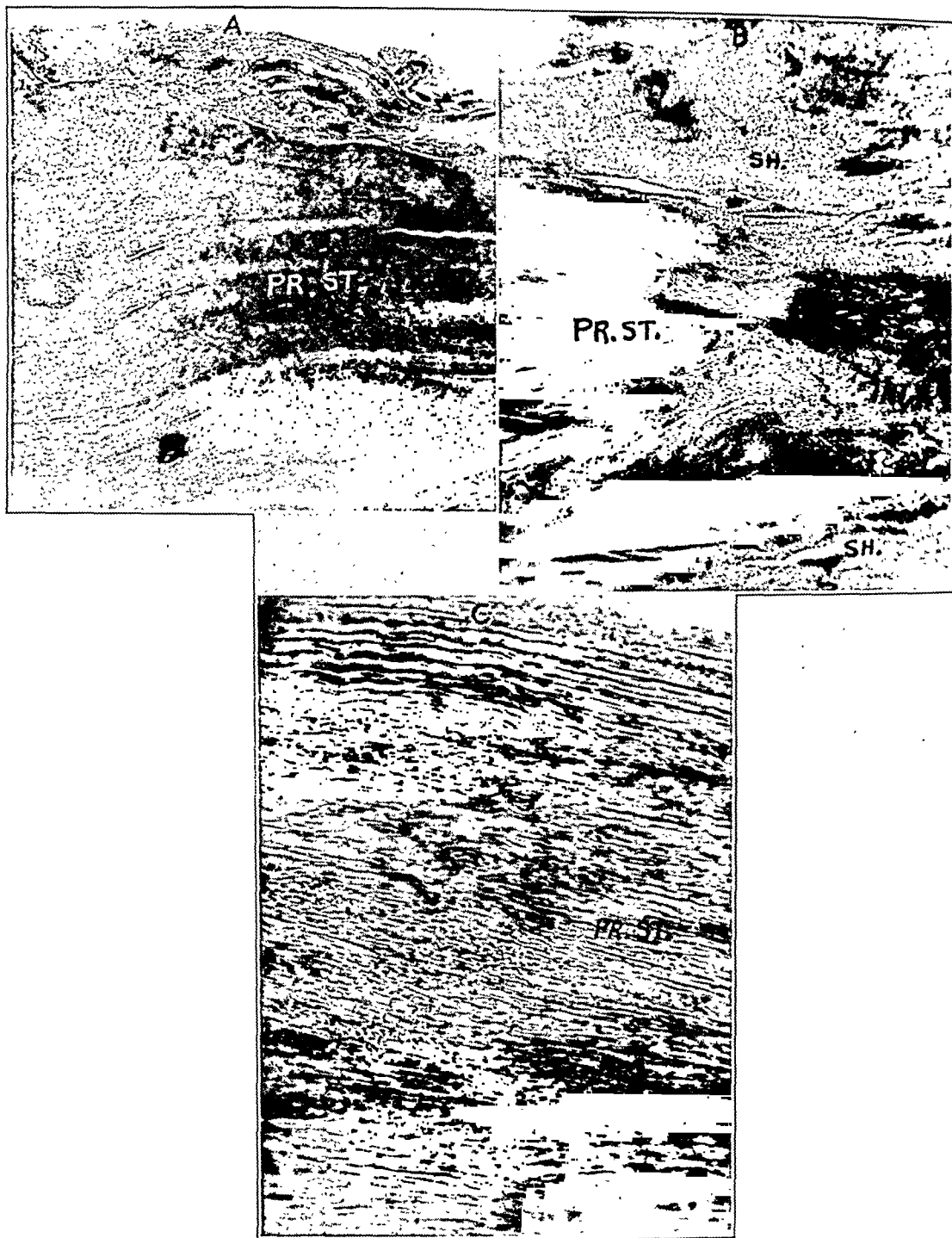


Fig. 13.—Photomicrographs of the proximal stump in a specimen removed from twelve to fourteen days after operation. *A*, the proximal stump (*Pr. St.*) of T 22 (fourteen days) shows the increased nuclearity of the tendon and the tendency for the fibers to straighten out. *B*, the proximal stump (*Pr. St.*) of T 23 (twelve days) tapers down into the intervening tissues (*Int. T.*) into which it sends proliferating fibers. The sheath (*Sh.*) has produced a thick dense union. *C*, under higher magnification the proximal stump (*Pr. St.*) of T 23 (twelve days) shows the characteristic increase in number of nuclei and blood vessels and the straightening of the tendon fibers.

When silk lay within the tendon it was sometimes surrounded by inflammatory cells, though in many places it appeared to lie directly against normal tendon or in an area of proliferating tendon. The silk itself was infiltrated with small round cells.

FOURTEEN DAYS.—*Dog T 22*.—Transplantation of a tendon graft plus its paratenon was made into a defect in the extensor carpi radialis. Apposition was good, but the graft frayed out a good deal. A cast was applied.

The dog was killed on the fourteenth postoperative day. The result looked quite poor; the distal suture line had separated, but the proximal suture line had held (fig. 25). Between the graft and the distal stump there was a good deal

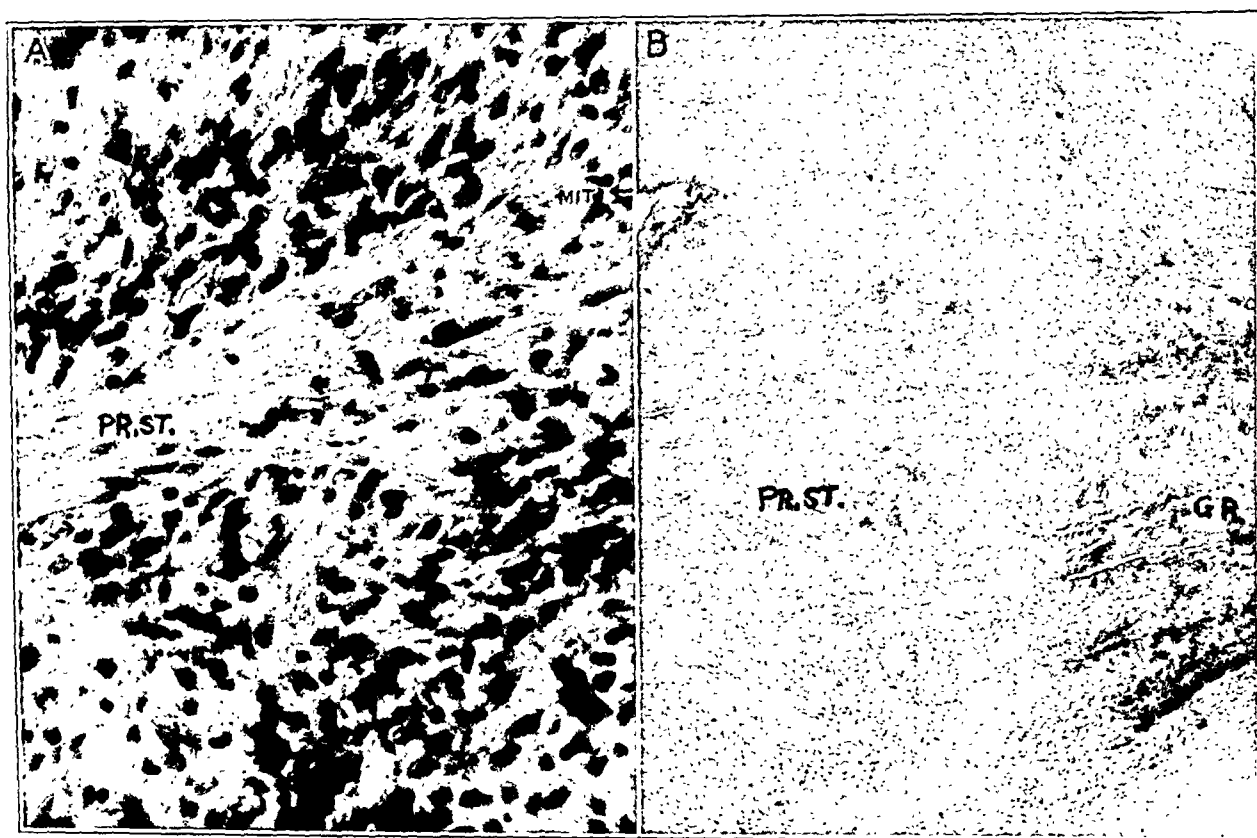


Fig. 14.—*A*, the distal end of the proximal stump of *T 3* (ten days) is sending numerous long tender proliferations of tenoblasts into the intervening tissues. Mitoses (*Mit.*) are frequent. *B*, in instances in which the separation between the stumps and graft has not been too great (*T 22*, fourteen days), the union across the intervening tissues is already quite strong. A photomicrograph under higher magnification is shown in figure 12 *B*. *Pr. St.* stands for proximal stump, *Gr.* for graft.

of connective tissue, through which pull on the muscle was not transmitted to the distal stump.

Microscopic examination showed that, although there was a separation at the distal suture line, the union at the proximal line was excellent (fig. 14 *B*). Unfortunately, the section was mishandled during cutting, and the distal stump had been lost. The proximal stump and the graft were practically in apposition and were

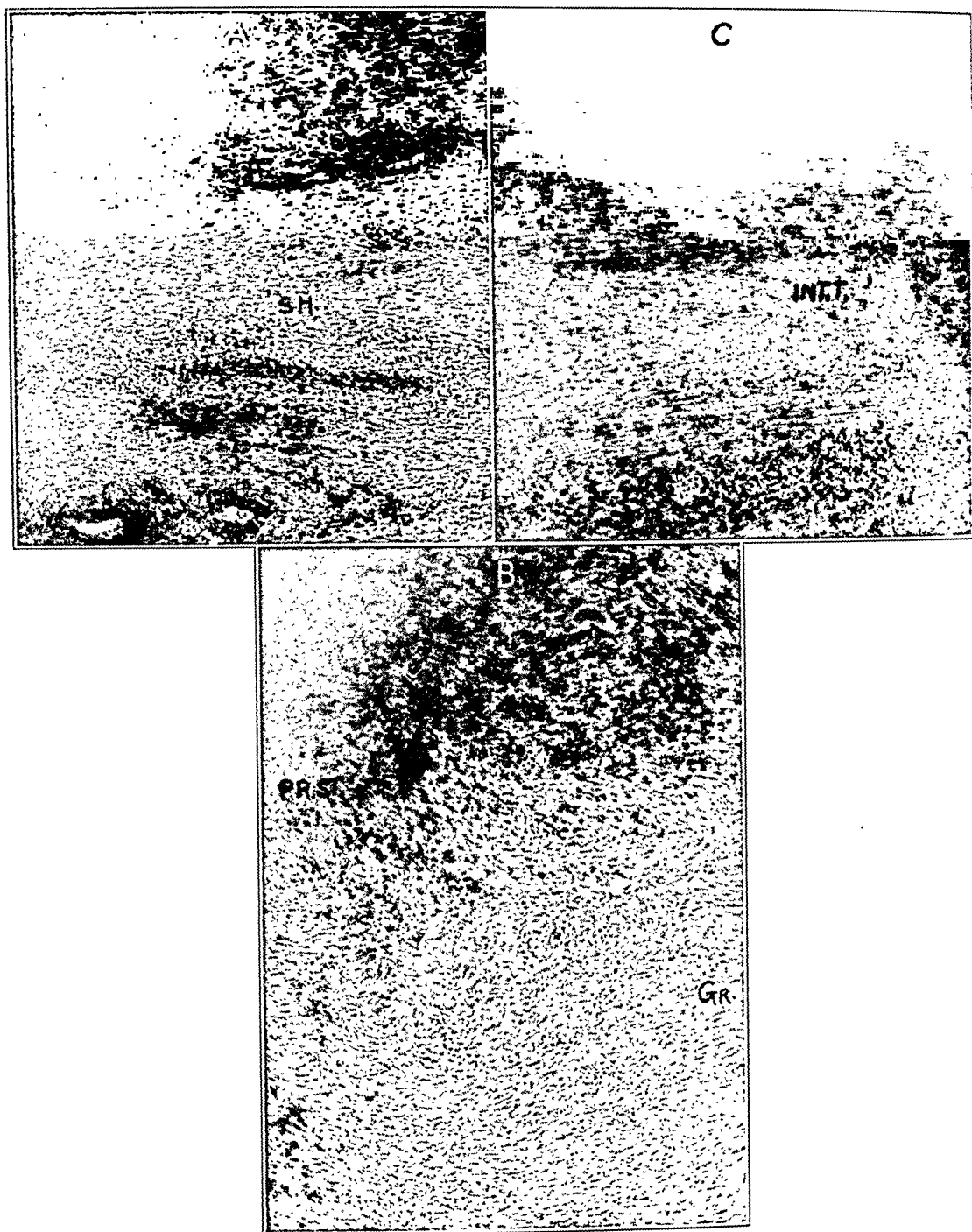


Fig. 15.—*A*, photomicrograph of the sheath over the intervening tissue in T 23 (twelve days). This is well organized and quite vascular. *B*, the tissue between the proximal stump (*Pr. St.*) and the graft (*Gr.*) in T 22 (fourteen days) have been solidly organized into a dense scar in which the tenoblasts from each tendon take part. *C*, the intervening tissue (*Int. T.*) of T 2 R (fourteen days) is organized into a dense tissue in which the fibers are arranged in long bundles parallel to the line of pull.

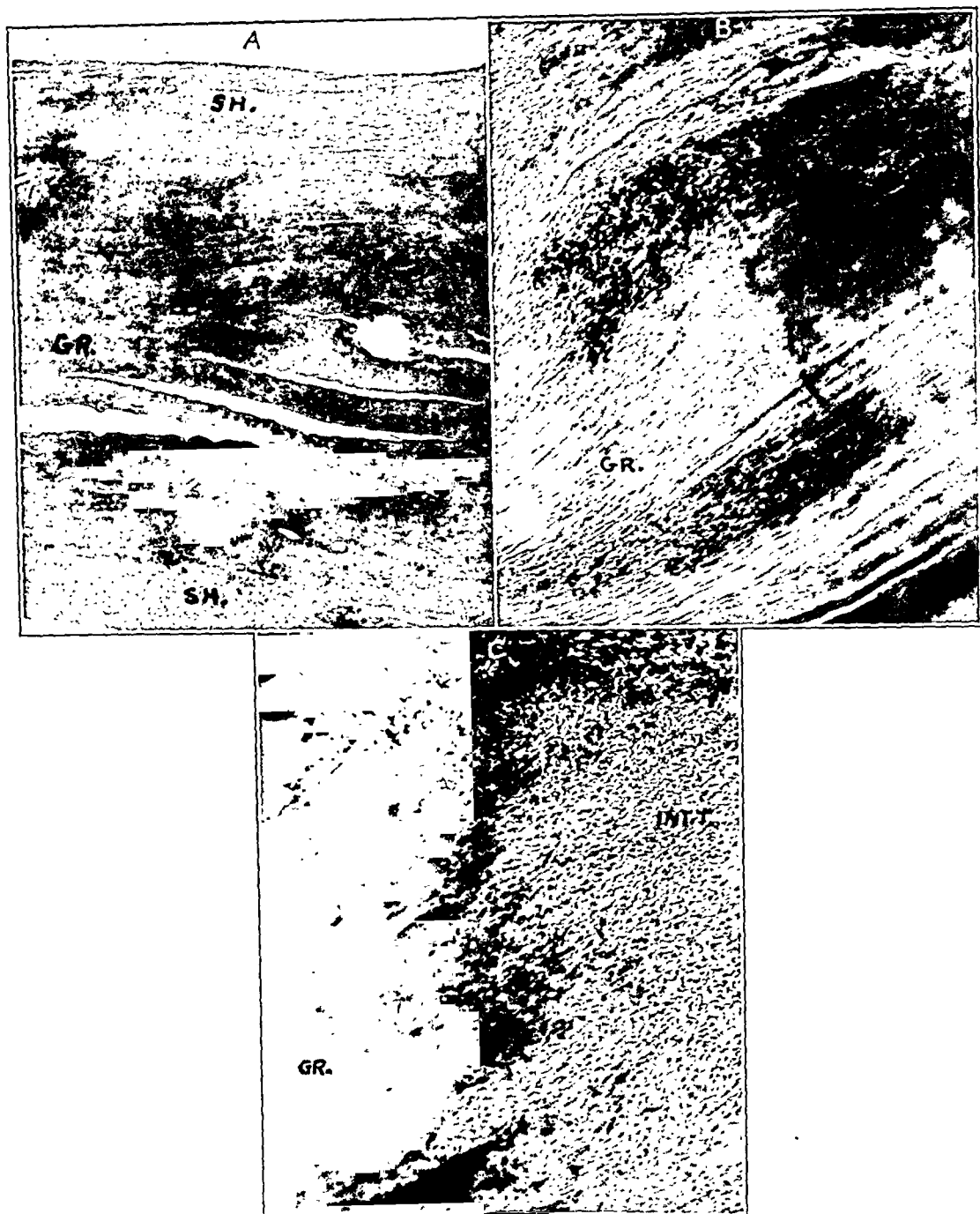


Fig. 16.—*A*, photomicrographs of the central part of the graft (*Gr.*) in T 22 (fourteen days), showing that it is practically entirely viable. Some of its fibers are still wavy, while others are straightening out. The sheath (*Sh.*) on either side is made up of longitudinally coursing connective tissue fibers. *B*, an area of the graft in T 23 (twelve days) showing the spotty character of the nuclear proliferation. *C*, the proximal end of the graft in T 23 (twelve days) is sending long prolongations of tenoblasts into the intervening tissues.



fused together solidly by a thin scar (figs. 14 *B* and 15 *B*) made up of tenoblasts proceeding from both graft and stump and of some granulation tissue. The proximal stump (fig. 13 *A*) showed nuclear increase throughout the length included in the section. This increase, as in previous sections, was not uniform, but occurred in bands throughout the tendon or in peculiar oval zones. One of these large zones was present several millimeters back from the end of the tendon and produced a definite widening of the tendon. The intratendinous vessels were increased, and the cells about them had proliferated. This proliferation about the vessels affected the peritenonium internum and the tendon itself. Considerable infiltration about the silk was present, but this was becoming organized, and a few giant cells could be seen in the tissues about the silk. From the end of the stump, rays of tenoblasts projected distally, some going directly toward the graft and there mingling with similar fibers from the graft, others passing to either side of the graft and ending in the proliferated sheath tissues.

The graft (fig. 16 *A*) appeared to have survived almost in its entirety and could not be distinguished histologically from the proliferating stump. It was quite vascular and appeared to be divided up into longitudinal zones by the numerous vessels which ran through it. There was cellular increase about these vessels. The nuclear content of the graft was increased, this increase, as in the stump, taking place in numerous zones or bands, running for a considerable distance throughout. These bands appeared (in stained section) much bluer than resting tendon, owing to the great nuclear increase in them. The silk had healed in nicely, though the tissue about the silk was not entirely fibrosed and still contained small round cells and giant cells. From the distal end of the graft, feather-like strands of tenoblasts pushed distally into the young fibrous tissue of the gap.

The sheath tissues in this specimen did not appear to be playing as important a rôle as they had formerly. There was very little sheath on the new tendon; it had presumably been split off in uncovering the specimen.

*Dog T 2.*—Transplantation of a segment of the extensor carpi radialis 3 cm. long, plus its sheath, was made into a defect of the opposite tendon. The graft was threaded over a double strand of silk, which was fastened by a lacing suture into each stump. No cast was applied. This procedure was carried out on the right leg.

The tendon (fig. 25) was examined fourteen days after operation. There was found a retraction of the stumps of about 1.5 cm. from each end of the graft. These spaces were filled with reddish-gray soft tissue that looked grossly like that in hematomas. The distal stump was slightly bulbous and had lost the pearly gray glistening appearance. There was some adherence of the sheath over the line of section. The proximal stump was also bulbous, and was soft and yellowish in appearance. Here too the sheath was adherent about the suture line. The graft was soft and lusterless. The hypertrophied sheath tissues appeared to bridge over the whole space between stumps and graft. On the under surface there was a dense band, probably mesotenon, running the whole length of the new tendon.

In this specimen, in which great separation had taken place, the manner of union differed from that in specimen T 22 of the same age. A considerable defect had to be bridged across, and here it was the sheath that had done it.

The stumps were separated approximately 3.25 cm. in the fixed specimen, and were united by a dense strand of very cellular and very vascular connective tissue which could be traced directly from the sheath tissues of either stump. This strand contained firmly embedded in its center a small bit of graft, about 0.4 cm. in length (fig. 25).

At the distal end of the proximal stump was an unorganized defect due to the knot in the silk. The stumps showed evidence of great proliferation, as evidenced by an increased number of blood vessels, an increase in nuclei and mitoses through the tendon and about the vessels. The nuclear increase was more marked nearer the suture line than away from the suture line. From the ends of the stumps proliferating strands of tenoblasts pushed into the intervening tissues to become lost in the fibrous and tendinous scar. The silk knot lying between the stump and the graft in the intervening tissue acted as a barrier to the tenoblasts.

The remnant of the graft showed increase in size and number of nuclei and the presence of occasional mitoses. From its ends there was proliferation into the connective tissues. The cells and fiber bundles of the graft were not as yet entirely oriented into a longitudinally arranged bundle.

The connective tissues forming the union (fig. 15 C) were arranged in longitudinal fashion, both fibers and nuclei, and in places it would appear that they were being divided into longitudinal bundles by blood vessels.

*Dog T 29.*—Transplantation of a 2.5 to 3 cm. tendon graft was made with satisfactory suture. A cast was applied.

The animal was killed on the fourteenth day. The superficial fascia and skin were easily dissected from the surface of the tendon; the proximal stump was conical and attached to the graft by a strand of silk covered with scar tissue. The distal stump was attached to the graft by a short stretch of silk also surrounded by scar tissue. The whole area was surrounded by thick strips of fibrous tissue which strengthened the union and were also somewhat adherent to the surrounding tissues. The strength of the union was tested by spring scale. The proximal stump pulled away from the end of the graft with a tension of  $11\frac{1}{2}$  pounds (5.2 Kg.).

Longitudinal section of the proximal stump showed a tendon of normal or resting histologic make-up in its proximal one-half. More distally, however, signs of proliferation were met with similar to those previously described. At the distal end of the stump the tendon fibrils pushed outward into the intervening tissues and mingled there with the connective tissue proliferation of the sheath.

The intervening tissue through which the rupture occurred (with a pull of  $11\frac{1}{2}$  pounds) was composed of condensed connective tissue which contained the silk suture. This connective tissue was still young and quite vascular. The tissue immediately surrounding the silk was organized, and the silk itself was infiltrated with small round cells.

An oblique longitudinal section taken through the graft showed this to be entirely viable. The silk lay in the tendon without any reaction about it and was infiltrated with small round cells. Except in the immediate vicinity of the vessels, and except for one area near one end of the graft, no evidence of tendon proliferation was seen.

A longitudinal section taken through an area of intervening tissues showed the silk suture embedded in tough connective tissue approaching the adult in type.

*SIXTEEN DAYS.—Dog T 3.*—Transplantation of a  $1\frac{1}{2}$  inch (3.5 cm.) segment of tendon graft plus its sheath was made into a defect left by removal of a  $\frac{3}{4}$  inch (2 cm.) segment. The graft was threaded over silk which was attached by lacing suture into each stump. No cast was applied.

The graft was examined on the sixteenth postoperative day. The skin and superficial fascia were removed easily after a fairly definite plane of cleavage was found. The silk was not visible on the surface.

Microscopic examination represented an early stage (sixteen days) in the formation of a tendon scar in a graft experiment in which there had been considerable

separation of graft from stump. The graft had only partially survived and made up but a small section of the tissues lying between the stumps. (The picture was similar to that of T 2).

Union had been effected in the manner described in the section dealing with tendon suture. The sheath tissues to either side of the stumps had proliferated proximally from the distal stump and distally from the proximal stump and had united with the proliferated sheath of the graft.

Large areas of the intervening tissue and of the tissue about the graft were filled with organizing granulation tissue and areas of hemorrhage. Brown pigment deposits liberally scattered throughout the tissue were evidence of resorption of red cells.

Although a large percentage of the graft appeared to have died, other parts showed an increase in the number of nuclei. At the ends of the graft this cellular increase had led to the production of feather-like strands of tenoblasts which were pushing out into the granulation tissue, filling up the gap. Mitoses were to be seen among the tenoblasts.

The tendon in the stumps was considerably altered. Areas of necrosis were present near the suture line. There was, however, an increase in nuclei in the non-necrotic parts of the tendons, and from the ends of the bundles strands of tenoblasts radiated outward into the scar (fig. 14 *A*). The endotenonium was also sending fibroblastic bundles into the uniting scar.

This then, so far, was a sheath union owing to the great gap that had to be bridged over. Tenoblastic proliferation, however, was becoming quite evident.

NINETEEN DAYS.—*Dog T 10*.—Transplantation of a 2 cm. tendon graft plus its sheath was made into a defect left by the removal of 1 cm. from the extensor carpi radialis. The graft was threaded over a silk thread which was attached to each stump by a lacing suture.

The dog was killed on the nineteenth postoperative day. There were no adhesions between the skin and superficial fascia and the underlying tendon. The distal stump was ruffled up as if too long for the space, and both stumps were slightly bulbous. The space between the stumps, measuring 3.5 cm., was bridged across by a small tough strand of white tendon-like tissue. The graft could not be identified as such, though in the center of this gap there was seen a yellow-white nodule of tissue which was thought to be a remnant of the graft. The tendon was quite adherent to the underlying bone, which had been stripped of its periosteum at the original operation.

The specimen examined microscopically followed in direct line those of dogs T 22 and T 23 and represented an excellent type of union in which both the stumps and the graft had taken part. Viewed casually, the whole regenerative tendon appeared to have a unified structure (fig. 26). Except for a short strip of resting tendon in the proximal stump, the whole of the tissues were very nuclear (fig. 17).

The whole of the tendon of the distal stump (fig. 17 *D*) was transformed into the highly nuclear young proliferating tissues that were seen in the earlier specimens. Mitoses were plentiful, especially as one passed from the distal end of the stump. The tendon was quite vascular. The passage from stump to intervening tissue to graft was almost imperceptible. It was possible to recognize the area of the graft only because of small areas of eosin-staining tissues.

The graft (fig. 17 *C*) was highly nuclear, and its strands of fibers were continuous at either end or at points that were assumed to represent the ends of the graft with fibers or cords of similar cells from the stumps.

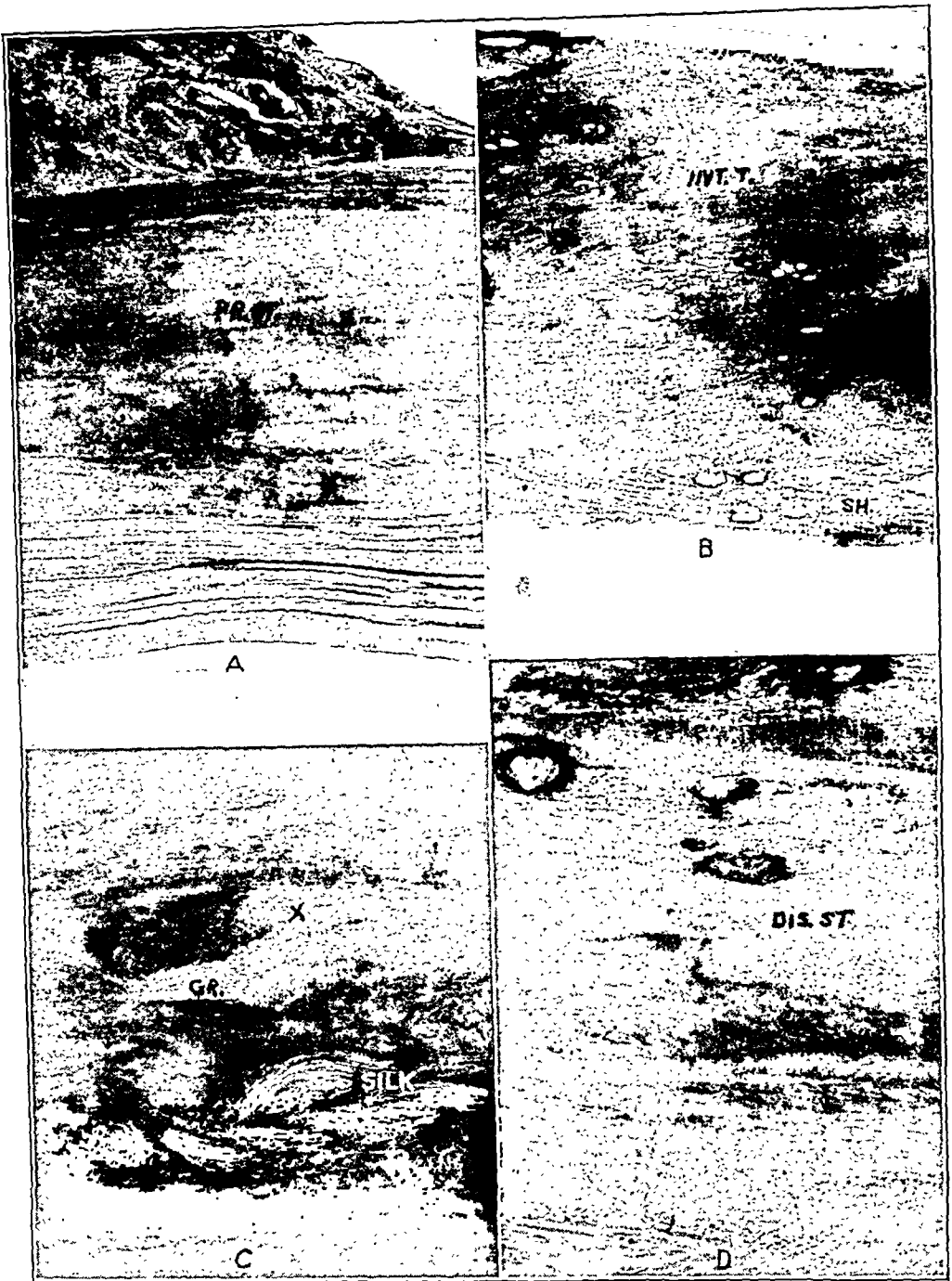


Fig. 17.—Photomicrographs through various areas of T 10 removed nineteen days after operation. The tissues are beginning to assume a remarkable sameness. *A*, the proximal stump (*Pr. St.*) is very nuclear; its fibers run in straight parallel lines and are divided into bundles by the intratendinous blood vessels. *B*, the intervening tissues (*Int. T.*) between the proximal stump and the graft are also lined up in long parallel rows. *C*, in the graft (*Gr.*) are a few areas (*X*) of the old deeply eosin-stained tendon. Most of it has undergone proliferative changes similar to those in the stumps. *D*, there has been somewhat less tendon proliferation in the distal stump.

The proximal stump (fig. 17 A) showed a small zone of nonreactive tendon, which, however, was more vascular than normal. The rest of the tendon had been converted into cellular proliferating tendon, from which strands passed distally into the intervening tissues.

All of these tissues, i. e., those of the stumps, intervening tissues and graft, were beginning to line up into longitudinally arranged bundles with blood vessels between them.

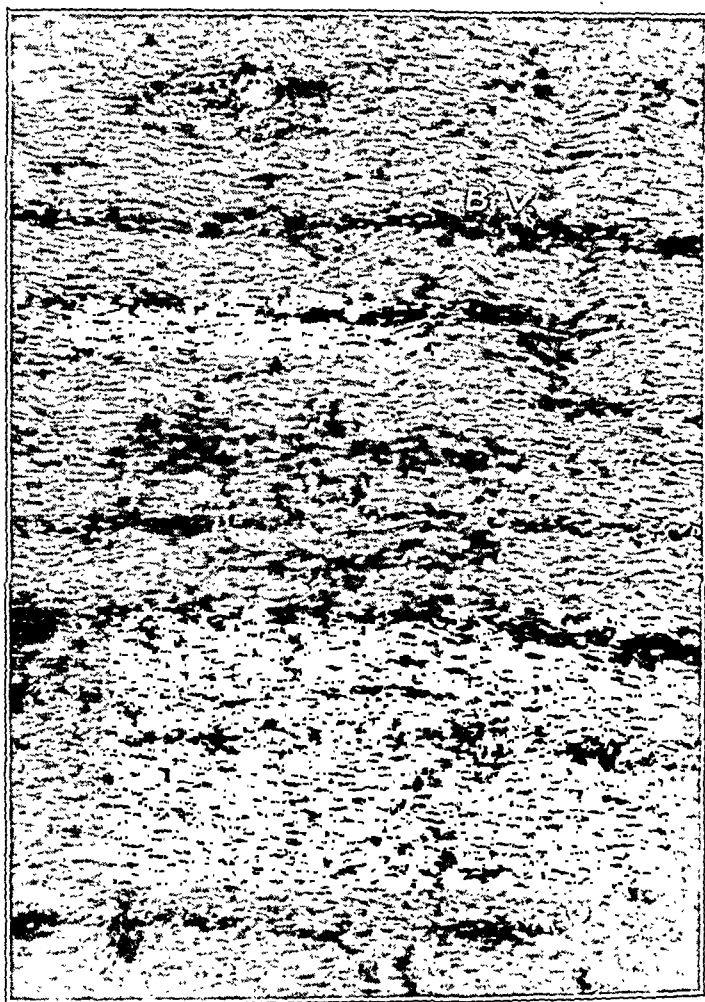


Fig. 18.—Photomicrograph of the tissue intervening between the graft and the proximal stump in T 18 (twenty-one days). The tissue made up of tenoblasts and fibroblasts is divided up into long parallel rows of very nuclear fibers by numerous longitudinal blood vessels.

TWENTY DAYS.—*Dog T 20.*—Transplantation of a 3 cm. tendon graft was made into a defect of the extensor carpi radialis left by the removal of 2 cm. of tendon. The graft was threaded over the silk suture, which was fastened into each stump by means of a lacing suture.

The dog was killed on the twentieth postoperative day. Considerable infection had developed, and the specimen was not examined microscopically.

TWENTY-ONE DAYS.—*Dog T 18.*—Transplantation of a 3 cm. tendon graft plus paratenon was made into a defect left by the removal of 2 cm. from the extensor carpi radialis. The graft was sutured into place by lacing sutures at each end and similar sutures in each stump. A cast was applied. The dog removed the cast himself two days later.

The dog was killed on the twenty-first postoperative day. The wound had healed nicely. The skin and superficial fascia were easily stripped from the surface of the tendon. There was direct and functional continuity between the ends of the stumps (fig. 26). The silk was not visible on the surface of the tendon. In the proximal stump there were seen numerous long red longitudinal streaks in the substance of the tendon.

The specimen examined microscopically was clearly made up of the two stumps with the intervening graft. It was seen that the separation at the proximal and distal suture line had been minimal, probably not over 0.5 cm. at either end. The region between stumps and graft was filled up with tissue which was in direct continuity with stump and graft.

The graft in its central parts was made up of very cellular tendon, divided by numerous blood vessels into longitudinal rows of closely packed fibers. Defect areas produced by the silk suture material within the graft were becoming organized into compact scar tissue, in the formation of which the tendon was taking part. At the ends of the graft the tendon bundles stained more lightly and were very nuclear. Long strands of tenoblasts pushed proximally and distally into the gap tissue and could be traced across this scar until they became continuous with similar strands from the stumps. This gap tissue was more vascular and arranged in less orderly manner than the graft tissues (fig. 18). It was made up of ordinary granulation tissue, of tenoblasts from graft and stumps and vacuole-like areas evidently caused by the silk.

The stumps had been almost entirely converted into proliferating tendon. Only here and there were there to be seen strands of old tendon fibers, and these were more numerous in the parts of the stump farther removed from the suture lines, i. e., in the proximal part of the proximal stump and distal part of the distal stump. The stumps had been considerably disturbed by the suture material, but this was now well healed in, surrounded by scar tissue in places and in other places by the proliferating fibers of the tendon. Around and about the buried silk, the tendon fibers pushed distally or proximally out into the scar of the gap through which they could be traced to become continuous with similar fibers from the graft. There was a general longitudinal parallel arrangement of the fibers in the stumps. This was broken up, however, by the presence of the suture material. The blood vessels in the stumps were markedly increased, and this applied especially to the longitudinal ones which divided the stump into longitudinal bands.

The sheath tissues were somewhat thickened and were continuous over the stumps and over one side of the graft. The outer layers of the sheath were loose and very vascular and apparently were taking over gliding function.

In this specimen there was repair mainly due to direct union between stumps and graft. The sheath had proliferated, but was now beginning to take over gliding function. The scar between stumps and graft was made up of organized granulation tissue plus tenoblasts, and the tenoblasts were apparently the major part.

*Dog T 19.*—Transplantation was done as in the preceding experiment on dog T 18. A cast was applied and stayed in place.

The dog died on the twenty-first postoperative day. The wound was clean and dry. The skin and superficial fascia stripped very easily from the surface of the

graft and stumps. The stumps and the grayish graft were in strong functional continuity. Pull on the muscle led to extension of the radiocarpal joint, with a range of motion of 90 degrees. There was a lax paratenon arrangement about the whole new tendon which permitted good motion.

Microscopic examination showed that there had been a separation of about 0.75 cm. at each end of the graft. These gaps, however, were bridged across by fairly solid tissue which at one place had been broken up by the microtome knife striking the suture material during sectioning. The tissue consisted entirely of tendon and graft with uniting gap tissues, no sheath having been removed from the animal, which corroborated the note that a paratenon-like arrangement was present.

In the main, the parts of the stumps at some distance from the suture lines looked like normal adult tendon. The tendon might have been somewhat more vascular and more nuclear than normal, but it stained deeply with eosin, its nuclei were very flat and deeply staining, and it was arranged in long rows of parallel fibers. Where the silk passed through these apparently normal areas of tendon, it was infiltrated with round cells and surrounded by scar tissue. Back from the ends of the stump there was little reaction of the tendon itself about the silk. As the end of the stumps was approached, however, the tendon was much more nuclear, and the deep eosin stain disappeared, owing to decrease in the amount of intracellular substance and increase in nuclei. Fibers of the tendon ran into the scar tissue of the gap. The nuclei in the intervening tissue, however, were beginning to flatten out and to become more mature. It is evident that, with similar infiltration of the intervening tissues from the side of the graft, the gap was being converted into a dense tenoblastic and fibroblastic scar. The silk and the knot had become somewhat solidly encased in the scar, though here and there one could see giant cells about silk fibers.

A large percentage of the graft had survived and was actively proliferating. It had been rather badly broken up by the suture material, which, however, was well healed in place. The graft was quite vascular, but its tissues were not nicely lined up as yet, owing presumably to disruption due to the suture material.

Here again there was union due to healing together of graft and stump ends by a dense scar in which the tendon cells of both graft and stumps had taken part. The silk suture had caused a certain commotion in the structure of the scar.

*Dog T 25.*—Transplantation of a 2 cm. tendon graft plus its paratenon was made into a defect left by the excision of 1 cm. from the extensor carpi radialis. The graft was threaded over two silk sutures, which were then laced into the stumps. The graft was too long, and it wrinkled up after being sutured into place. A cast was applied.

The dog died on the twenty-first postoperative day, and postmortem examination was not made until the day following. The tissues could be stripped easily from the tendon. It was found that the suture had pulled out at the proximal suture line, and that there was a separation here of 3 cm. The graft was securely attached distally. The proximal defect was bridged with a thin scar which broke very easily on slight pull. No microscopic examination was made, since the tissues had been too long unpreserved.

*Dog T 2.*—Transplantation of a  $1\frac{1}{4}$  inch (3.1 cm.) segment of tendon plus sheath was made into a defect of similar length in the extensor carpi radialis. The graft was threaded over a silk suture which was laced into each stump. No cast was applied. This procedure was carried out on the left leg.

The animal was killed on the twenty-first postoperative day. The tissues over the line of graft were bound to the operative area by dense adhesions which had to be removed by sharp dissection. Between the stumps, which had separated 4.5 cm., was a swelling which when opened was found to contain about 5 cc. of bloody fluid

and a few strands of white tissue. To the lateral side of this cavity and in direct continuity with it was another cavity in which the silk suture was found. The specimen was carefully removed and placed in formaldehyde.

Microscopic examination showed that considerable separation had taken place between stumps and graft, and a rather insecure union had been effected by a band of connective tissue along one side of the structure. The graft was definitely recognizable, was largely necrotic and was invaded by blood vessels and lymphocytes. Even in the most infiltrated areas, however, one could see large oval, vesicular, active, tendon nuclei with occasional mitoses as evidence of tenoblast formation.

The stumps were much more vascular and considerably more nuclear than the graft. This proliferation was most evident in the proximal end of the distal stump and the distal end of the proximal stump, where nearly the whole of the tendon was converted into a densely cellular structure. Further back from the suture lines the areas of cellular increase were distributed, bandlike, throughout the tendon. Along the side of the stumps from which the sheath proliferation proceeded, the tenoblasts tended to follow out somewhat along the line of tendon pull. Opposite this area, however, the arrangement of tendon nuclei was more irregular.

The proliferated and moderately thickened sheath was continuous from stump to stump, having fused with the thickened sheath tissues of the graft. The sheath was highly vascular, and only in places was it lined up in longitudinal parallel rows.

**TWENTY-TWO DAYS.—Dog T 1.**—Transplantation of a 1½ inch (3.8 cm.) segment from one extensor carpi radialis was made into a defect left by the removal of a similar segment from the same tendon on the opposite leg. The graft was threaded over a double strand of number D twisted silk, which was secured by lacing sutures into each stump. No cast was applied. Reciprocal graft was made into both legs, and the sheath closed carefully.

The animal was killed on the twenty-second postoperative day and both specimens were removed. On the left leg, the graft apparently had been replaced by scar tissue (fig. 26) in which a few fibers, apparently tendon, were still visible. The whole area was densely adherent and immovably bound down in scar tissue. Both of the stumps were bulbous, the distal more so than the proximal. The sheath over the stump appeared normal. On the right leg, the conditions were about the same, except that the adhesions were somewhat less marked.

**Dog T 1.**—The microscopic picture was complicated by the presence of the crossing tendon of the extensor pollicis longus. This had become embedded on the surface of the replacement tendon (Ersatzsehne [Schwarz]) and showed a moderate increase in nuclei. This procedure was carried out on the right leg.

Both stumps had been converted into very nuclear and vascular irregular bands of proliferating tendon tissue. The nuclei, which were so numerous that the tissue stained quite purple with hematoxylin, were oval and elongated, much fatter and more lightly staining than resting tendon nuclei. Mitoses were to be seen well scattered throughout the stump.

The nuclei were beginning to be arranged in longitudinal fashion, parallel to the line of pull, but the vessels were only beginning to show this longitudinal arrangement. The line of fusion between the stumps and the tissue uniting them was much less distinct than in any previous specimen. In general, the stumps were more nuclear than the intervening tissue. This scar of intervening tissue was made up of fibrous vascular connective tissue, plus prolongations from the ends of the stumps. It also contained the proliferating graft.

It was difficult to recognize the graft tissue definitely as such, owing to the complicating factor of the crossing tendon. Still there was one location in the unit-



ing tissues that presumably represented the graft. It was made up of very vascular bundles of fairly deeply eosin-stained fibers with numerous oval vesicular nuclei among which mitoses were to be seen quite similar to the proliferating tendon of the stumps. It too was being lined up in longitudinal bundles parallel to the line of pull.

*Dog T 1.*—Microscopic examination showed that here (the left leg) the differences between the various segments of the replacement tendon had almost disappeared. It was still possible to recognize the proximal stump as such, but the distal stump, graft and intervening tissues were blended into a unified whole. The differences between the proximal stump and the remainder of the tendon were more apparent on gross examination of the slide than they were on microscopic examination. A few strands of deeply eosin-stained nonproliferating tendon fibers were still visible, but most of the stump had been converted into bands, whorls and oval masses of very nuclear proliferating tendon. Where this proliferation was the most marked it had resulted in an increase in diameter of the tendon, hence its bulbous end. This bulbous end tapered down slightly and ran with practically imperceptible histologic change into the intervening tissues.

The proximal stump was quite vascular, the vessels, while running for the most part longitudinally, also ran to some extent transversely and obliquely across the tendon. Changes were beginning to appear in the nuclear areas of tendon. Some of these areas, those most deeply stained with hematoxylin, resembled those present in the earlier specimens, i. e., the nuclei were oval and fat, quite vesicular, and the eosin-staining intercellular material minimal. However, in the other areas, there began a flattening of the nuclei, an increase in the amount of eosin-staining intercellular material and a more adult appearance to the tissue.

The tissue between the stumps had taken on a uniform character. The location of the graft was still betrayed by the presence of a small area of deep eosin-staining fibers; otherwise the whole stretch was made up histologically much the same as the stumps. There were numerous blood vessels, running partly transversely and obliquely in the tendon, but the majority were longitudinal and were beginning to divide the tissue into longitudinal bundles. The nuclei throughout the central part were elongated, oval or cigar-shaped, vesicular and faintly staining. There was considerable eosin-staining substance making up the fibrous-like bundles of which the new tendon was composed.

Where silk lay in either the stumps or in the replacement tendon it was firmly embedded, though infiltrated with round cells. Occasionally, numerous foreign body giant cells were seen about the silk.

The sheath tissues had been removed at the time the specimen was excised. They separated easily and formed no integral part of the union.

*TWENTY-FIVE DAYS.—Dog T 13.*—Transplantation of a 1.25 cm. graft was made into a defect of the extensor carpi radialis left by the removal of 1 cm. of tendon. The graft was threaded over a double strand of grade D twisted silk which was laced into each stump. No cast was applied. The sheath was not closed, and the area was covered by the superficial fascia.

The animal was killed on the twenty-fifth postoperative day. The area between the two stumps was filled by scar tissue which was adherent (fig. 26). A fibro-gelatinous sheath appeared to be forming over the new tendon. This sheath, when opened, was found to be adherent to the connecting scar, but allowed a certain degree of motion through it.

The proliferating changes in and about this replacement tendon had been enormous, so that the resultant structure was very thick and broad. The graft

had been strung over a double strand of silk which was still visible. The stumps could still be identified as could also the region of the graft, but they were all becoming unified into a structural whole. Except for the great size of the tendon, the tissue had the same histologic characteristics as those just described for dog T 1 L.

*Dog T 12.*—Transplantation of a 1.5 cm. graft taken from one extensor carpi radialis was made into a defect left by removal of 1 cm. from the other extensor carpi radialis. The graft was threaded over a double silk suture which was secured by lacing suture into the stumps. No attempt was made to close the sheath, and no cast was applied.

The dog was operated on again twenty-five days after the graft was made. The result was poor. There were massive adhesions between the skin and tissues between the stumps. The area between the stumps was replaced by a scar in which the suture was embedded. The suture had pulled out from the distal segment, but was still attached proximally.

Microscopic examination showed that in this specimen the proliferating changes in the proximal stump were marked, though there had been a good deal of disruption here owing to the silk, which was, however, firmly embedded. The gaps between the stumps and graft had been quite large, but they were successfully bridged across by proliferation on the part of each stump and graft so that there was direct continuity between graft and stumps. The nuclei throughout were beginning to flatten out somewhat, but were still numerous. Only rarely were mitoses seen. The alignment in general was parallel to the line of pull, but this was not so well arranged as in other specimens.

**TWENTY-EIGHT DAYS.**—*Dog T 9.*—Transplantation of 2 cm. of tendon graft plus sheath was made into a gap of 1.9 cm. left by removal of 1 cm. from the extensor carpi radialis. The graft was threaded over a double strand of silk which was secured into each stump by lacing suture. The sheath was closed, but no cast was applied.

The animal was killed on the twenty-eighth postoperative day. There was a small healing ulcer over the incision which was slightly adherent to underlying structures, but not adherent to the area of the graft. The stumps, which were separated 3.5 cm., were united by a thin rounded strand of tissue, which, however, did not look like graft. The distal stump was white and ruffled up somewhat as if too long for its space. The proximal stump was bulbous and tapered off into the intervening tissues. The whole area was densely adherent to the underlying bone, but not adherent to superficial fascia.

Microscopic examination showed that healing had taken place despite the ulcer on the leg. However, the presence of infection had complicated the picture considerably. The graft had only partially survived the ordeal. Both stumps and the graft, however, were proliferating despite the great amount of organizing granulation tissue that was surrounding them, and union had been secured.

**THIRTY-ONE DAYS.**—*Dog T 28.*—Transplantation of a graft about 2.5 cm. long plus its paratenon was made into a defect of the extensor carpi radialis. The graft ends were secured in the stumps by means of lacing sutures. The sheath was not closed. A cast was applied.

The leg was reopened thirty-one days after this operation. A successfully functioning tendon was present (fig. 19). The stumps were bulbous, swollen and grayish. They were united by a bulbous strand in which the graft was undoubtedly embedded. There had been some separation at each end, but the amount could not be determined, since the ends of the tendon could not be ascertained. The tendon

pulled easily through the surrounding tissues and was subjected to a pull of slightly more than 40 pounds (18.1 Kg.) before rupturing. The break took place through the junction of the graft with the proximal stump.

Microscopic examination of a cross-section of the distal stump in this instance showed that the tendon was more nuclear than normal, although this increased nuclearity was by no means uniform. One large bundle making up one third of the tendon was hardly distinguishable from normal adult tendon, except for an increase in cells about the intratendinous vessels and an increased number of these vessels. The silk lay embedded in a narrow zone of connective tissue, infiltrated with small round cells, while here and there giant cells were seen about it. All of the tendon was more vascular than normal, and it was possible to trace small vessels from the surrounding sheath into the superficial surface of the tendon. Mitoses were still present in the area of tenoblastic increase, but were much less frequent than in earlier specimens. The sheath appeared to have been very loosely connected, since it had been practically all removed.

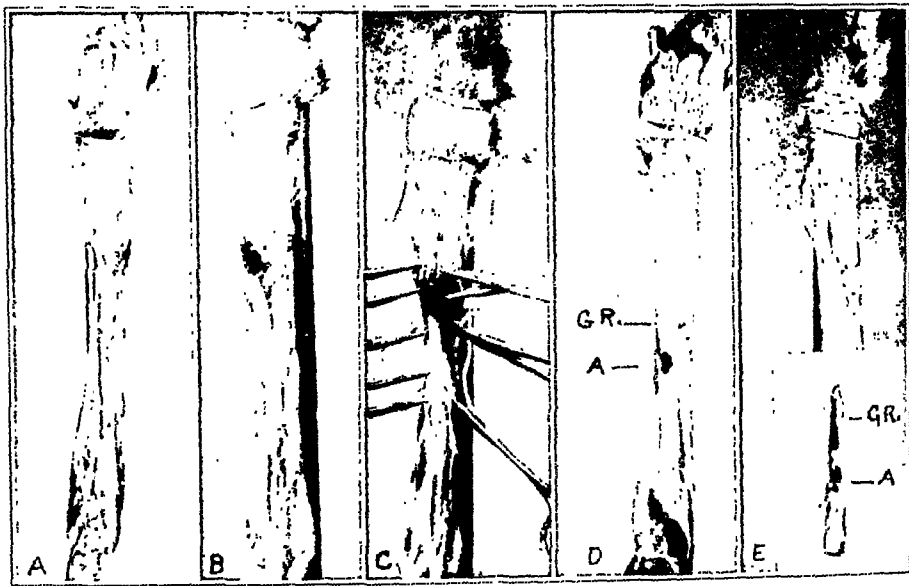


Fig. 19.—Gross specimens removed thirty-one (*A*, T 28), thirty-three (*B* and *C*, T 31) and thirty-five (*D* and *E*, T 27) days after operation. The sheath has been dissected away from T 28. In the first specimen of T 31 (*B*), the sheath is shown still covering the tendon; in the second photograph of this specimen tendon. In the first photograph of T 27 (*D*), the proximal suture line at point marked *A* shows up as a dark area, owing to its vascularity. This tendon ruptured at 36 pounds (16.3 Kg.) pull, not, however, through the rather weak looking suture line, as shown in the second photograph (*E*) of the specimen.

A cross-section of the graft showed it to be made up almost entirely of young or proliferated tendon. Only here and there were areas of old normal adult tendon to be seen. The striking feature of the section was the exact delimitation of the regenerating or replacement tendon. It lay as a separate definite entity of uniform histologic make-up, quite distinct from the surrounding sheath tissues. Although this sheath was connected with the replacement tendon of the graft along a good deal of its circumference, one particularly large strip of tissue was entering the tendon from the sheath, which reminded one of a mesotenon. Mitoses could be seen in moderate numbers in the graft.

The proximal stump had been entirely converted into proliferating tendon, and was made up of areas of very nuclear tendon bundles, for the most part cut transversely, though some were cut longitudinally and obliquely. Mitoses were present, but were not so numerous as in earlier sections, and the nuclei did not appear to be so large. The sheath surrounded the tendon as a distinct structure, more vascular and more loosely constructed. The synovial layer between sheath and tendon was not apparent, but a paratenon arrangement evidently accounted for the mobility. The suture was firmly embedded, and along the periphery was invaded here and there by strands of cells.

**THIRTY-THREE DAYS.—Dog T 31.**—Transplantation of a graft slightly over 3 cm. long was made into a similar defect in the extensor carpi radialis. The graft was secured to the stumps by means of lacing sutures. The sheath was not closed. A cast was applied.

The animal was killed on the thirty-third postoperative day. There was found a well developed fibrous sheath through which the graft moved easily, and which could be dissected away as a separate distinct layer from the underlying new tendon (fig. 19). Both stumps were enlarged and bulbous. They were firmly united to the graft by short segments of solid tissue (there had been a slight separation at each end of the graft). A pull of 35 pounds (15.9 Kg.) broke through the graft at the distal suture line.

Microscopic examination of a specimen showed that the three segments of the replacement tendon were present as three bulbous enlargements, each of which contained some areas of adult tendon, though made up mainly of proliferating tendon.

The gap between the proximal stump and the graft was bridged by a rather narrow strand of tough tendon-like tissue, in the center of which a length of silk lay embedded. The silk had been broken out by the microtome knife during sectioning and hence had left a long defect.

There was no line of demarcation between the graft and stumps and this intervening tissue. The fibers from the tendon of each structure passed directly over into the intervening regenerated tendon.

The nuclei in the proliferating parts of the tendon (fig. 20 *A* and *C*) were flattening out, though they were still more oval and larger than in normal adult tendon. Parallel longitudinal arrangement was present in the fibers making up the intervening tissue (fig. 20 *B*) as well as the proliferating areas in stumps (figs. 20 *A*, 21 *B* and *C*) and graft (fig. 20 *C*).

The suture material in the tendon was solidly healed in, and infiltrated slightly with round cells. At the point of rupture of the tendon at the distal suture line, the silk had made a large central defect in the replacement tendon. The tissues passing to either side of the silk were neither so dense nor so heavy as at the proximal suture line. Only thin strands of tendon fibers could be traced through it from the graft.

**THIRTY-FOUR DAYS.—Dog T 7.**—Transplantation of a 2 cm. length of extensor carpi radialis plus its sheath and mesotenon was made into a 1.8 cm. gap left by the removal of 1 cm. from the opposite tendon. The graft was threaded over a double strand of number D twisted silk which was secured into the stumps by lacing sutures. The sheath was carefully closed over the area by fine silk sutures.

The animal was killed thirty-four days following the operation. There was an ulcer over the incision, but this was lateral to the graft. The superficial fascia was stripped easily from the area of operation. There was separation at each end of the graft. The proximal stump had retracted considerably, the muscle belly

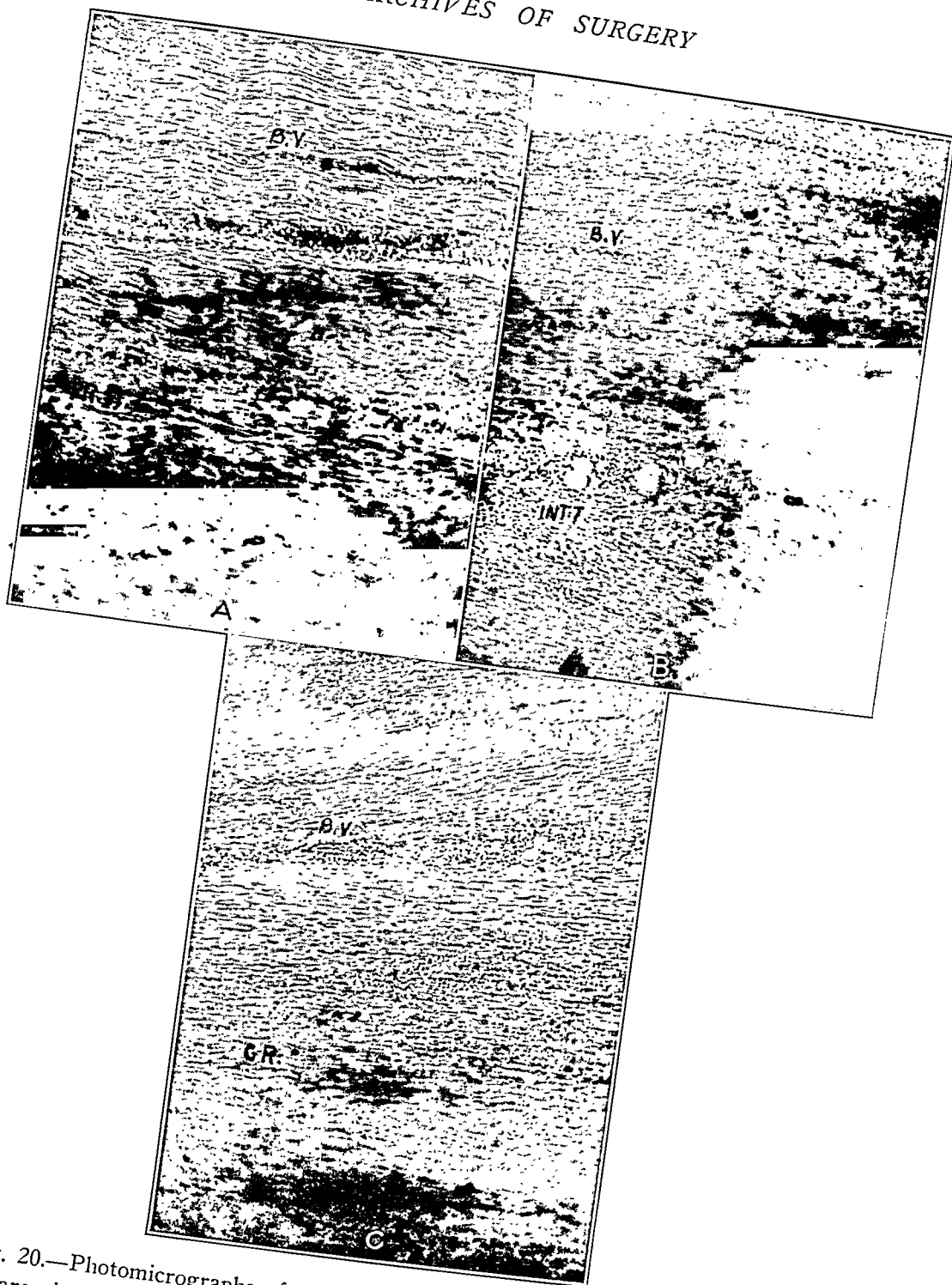


Fig. 20.—Photomicrographs of tissue removed from T 31 (thirty-three days). *A*, an area in the proximal stump (*Pr. St.*). The tendon nuclei are increased in number, but are flattening out. The intratendinous blood vessels (*B. V.*) are numerous, and there is an increase in cells about them. *B*, tissue intervening (*Int. T.*) between the proximal stump and the graft. It is also lined up in long parallel rows with numerous blood vessels. *C*, an area of the graft (*Gr.*) which shows the longitudinal arrangement of the tendon fibers, their increase in nuclei and the nuclear increase about the blood vessels.

was smaller than normal and appeared atrophic. The distal stump was grayish-white and ruffled up. The stumps were united by dense scar tissues adherent to the bone; in the center lay the graft.

**THIRTY-FIVE DAYS.—Dog T 27.**—Transplantation of a tendon graft plus paratenon was made into a defect of the extensor carpi radialis. The graft was secured by lacing suture into each stump. The sheath was not sutured; a cast was applied.

The animal was killed on the thirty-fifth postoperative day. The resultant tendon (fig. 19) functioned excellently. After all other tendons capable of extending the foot had been cut, the new tendon could completely extend the joint by pulling on the muscle belly. The graft appeared viable, lay in place between the stumps, and was securely attached to them. About the whole area were sheets of connective tissue which could be easily stripped from the tendon and which

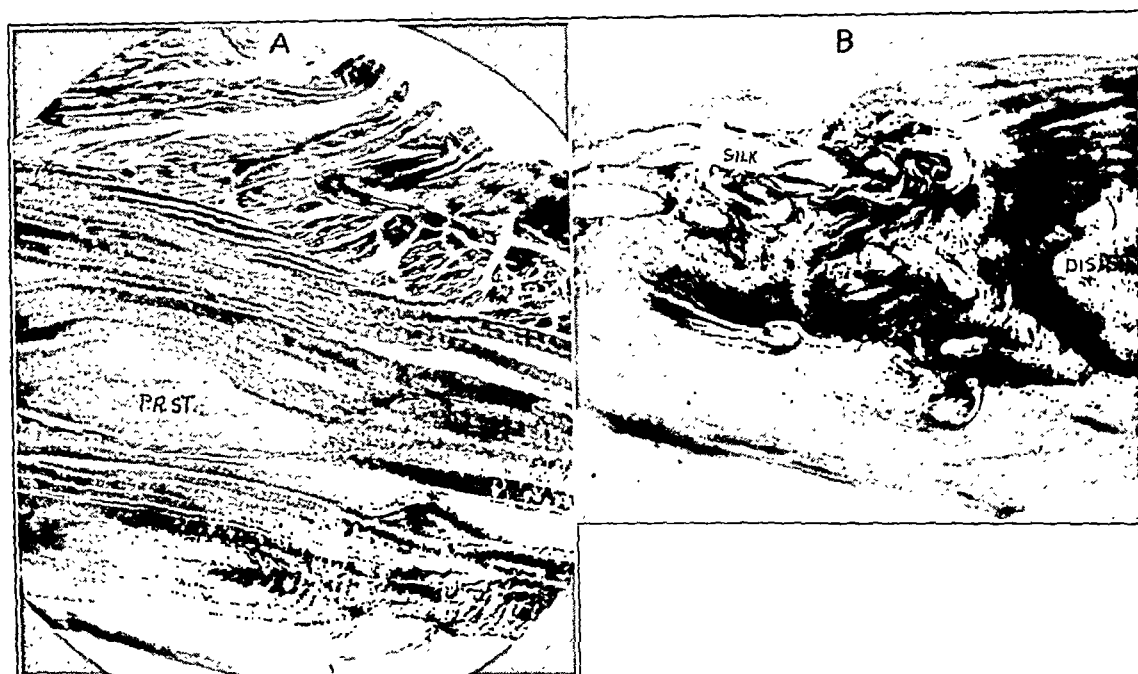


Fig. 21.—Low power photomicrographs of the proximal stump, *A*, and distal stump, *B*, of T 31 (thirty-three days). In the proximal stump the straightening of the fibers is well shown. In the middle of the stump is seen a large oval area in which tendon proliferation has been especially rapid. In the distal stump the silk has caused considerable disturbance of the tendon fibers, but the area here shown is well organized.

allowed very free movements. Before these sheets were separated from the tendon, a pull of 50 pounds (22.7 Kg.) failed to rupture it. After the surrounding paratenous tissues were divided, a pull of 36 pounds (16.3 Kg.) broke the tendon at the junction of graft and distal stump.

Microscopic examination of a cross-section of the proximal stump showed that the tissue was divided into a number of bundles practically all of which were cut exactly transversely, in comparison to earlier specimens in which, on cross-section, the section was seen to pass obliquely or evenly longitudinally through some bundles. Only here and there were very small areas of adult tendon seen; practically the whole section was a younger tendon, very nuclear. The nuclei were

oval or round, not so large and more darkly staining than in earlier stages of proliferation. Mitoses were not seen. The intratendinous connective tissue septums were quite thick in places. The sheath was a distinct paratenon-like structure and loosely bound to the tendon. There was no synovial membrane.

Cross-sections through the graft presented essentially the same picture as did the proximal stump. The blood vessels running through the graft were more numerous than in the stump. There were several areas in which gaps in tendon tissues were being filled with organizing granulation tissue.

The sheath was a perfectly distinct paratenon-like structure with a suture embedded in it at one place. The suture here was surrounded by granulation tissue containing giant cells.

The distal stump was also made up of very cellular bundles of fibers, cut for the main part transversely. It was more nuclear and arranged with less order

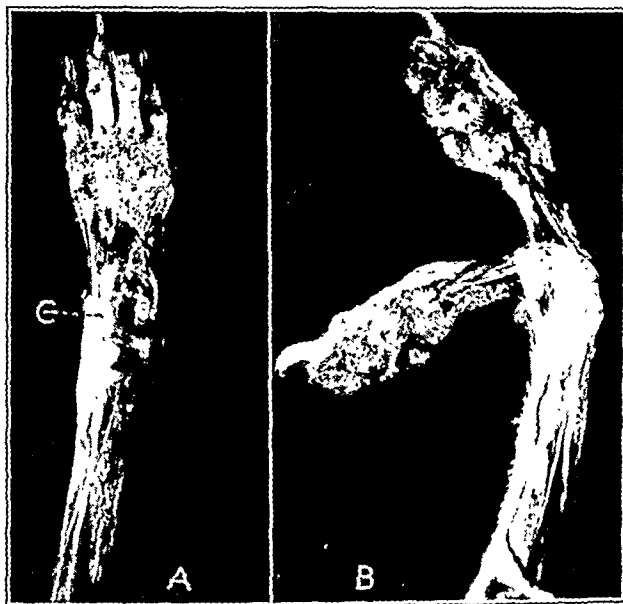


Fig. 22.—Photographs of the gross specimen T 11 (one hundred days). The replacement tendon is well shown in *A*. In *B*, the function of this tendon is shown by laterally superimposed exposures. *C* stands for replacement tendon.

than either the graft or the proximal stump. The sheath surrounding it was quite distinct from the tendon, though no synovial membrane was present.

**SEVENTY DAYS.—Dog T 16.**—Transplantation of a 2 cm. graft plus paratenon was made into the gap of the extensor carpi radialis left by the removal of 1.5 cm. of tendon. The graft was laid in place by side-to-side suture. The defect was longer than the graft, and the distal suture line was bridged by sheath. No cast was applied.

The dog died seventy days after operation. There was purulent arthritis of the radiocarpal joint, and a large encapsulated bag of pus lay under the area of the graft. The distal suture line had separated entirely. The proximal suture line still held, but the stump and graft were pushed ulnarward by a collection of pus.

Microscopic examination showed that, despite the infection, parts of the graft had survived, so that in its area was a large bulbous enlargement, made up of proliferated graft plus the organization of exudate. The proximal stump and

graft were firmly united by a strand of tissue which was quite thin in its central parts, but which broadened out at each end where it approached and became continuous with the stump or graft.

The tendon of the graft and the replacement tendon were very vascular and very nuclear. They were made up of long parallel strands of nuclear tissue (tendon), in which the fibers and nuclei were lining up in a direction parallel to the line of pull. Evidently, despite the abscess and arthritis, the tendon was pulling against some distal attachment.

Nothing of the distal stump was recognized.

ONE HUNDRED DAYS.—*Dog T 11.*—Transplantation of a 2 cm. length of extensor carpi radialis plus the sheath was made into a gap left by the removal of 1 cm. from the opposite extensor carpi radialis. The graft was threaded over a double strand of number D twisted silk, which was secured to the stump by lacing

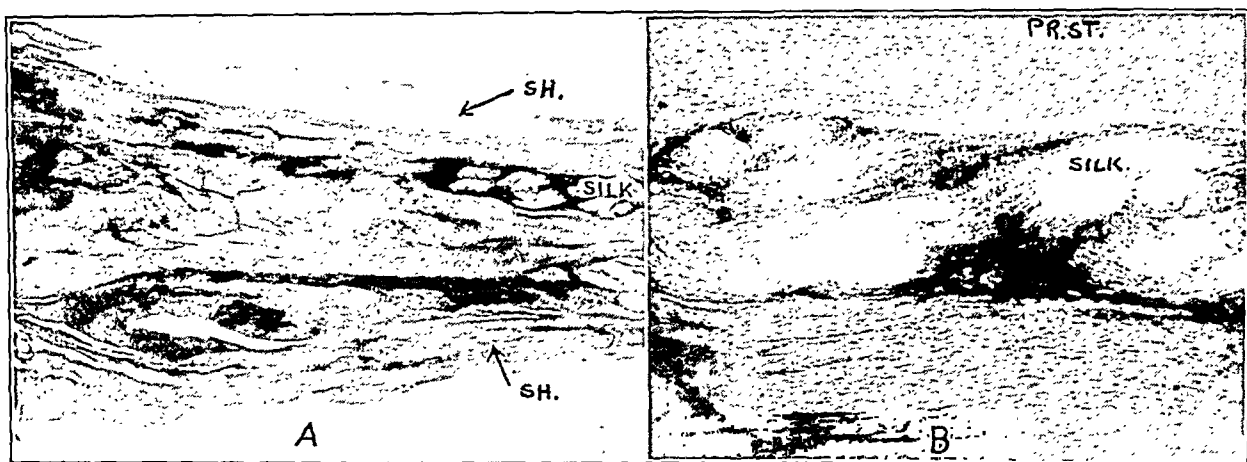


Fig. 23.—Photomicrographs of the proximal stump of T 11 (one hundred days). *A*, under low power magnification, shows the great vascularity of the proximal stump and its dense organization. The silk here has been well incorporated into the stump. The sheath along one side is thin and loose, along the other side thick. *B*, an area of the proximal stump under higher magnification. The silk is infiltrated with white cells, but there is no growth into it of tendon fibers.

sutures. The sheath was carefully closed over the suture lines. No cast was applied.

The dog was killed on the one hundredth postoperative day. He had excellent function in the leg on which operation had been performed. The skin and fascia were stripped from the replacement tendon with ease. The muscle belly was red and but slightly smaller than normal. Over the area in which the graft had been placed was a strand of silk, firmly embedded in dense white tissue. Overlying the whole area were thin fibrous sheets which were very lax and allowed the replacement tendon to move freely (fig. 22). The knot was seen in the distal stump about 1.5 cm. from its end.

Microscopic examination was made. The specimen (fig. 26) was a unified whole, showing the same histologic structure throughout, so that it was not possible



to distinguish graft from stumps and intervening tissue. It was made up of long continuous strands of dense tendon tissue (figs. 23 and 24), between which ran longitudinal blood vessels. The tendon fibers ran a straight parallel course for the most part, except when they passed around silk suture material. The nuclei were thin and flat, parallel to each other and to the course of the tendon fibers. Blood vessels were plentiful, not all of them longitudinal, but, in the regions of the stumps, transverse as well. The silk lay firmly embedded, infiltrated with small round cells. There was no longer any reaction around it.

The sheath had been removed, but there was no evidence of synovial membrane on the surface of the tendon.

The ends of this new tendon were somewhat bulbous in contrast to the narrow central part; this was the only suggestion of the one time location of the stumps. It was not possible to say whether the graft had survived or not.

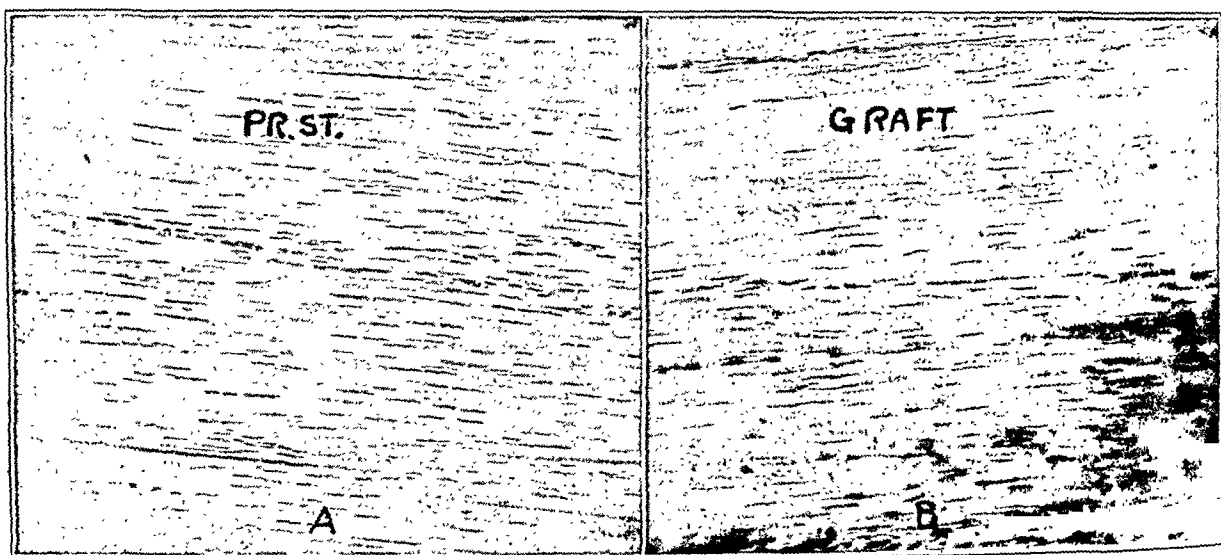


Fig. 24.—Photomicrographs under high power magnification of the proximal stump, *A*, and the region of the graft or replacement tendon, *B*. It is practically impossible to distinguish these areas from each other microscopically.

#### THE PROCESS OF REPAIR IN A TENDON GAP BRIDGED ACROSS BY A TENDON GRAFT

Microscopic study of specimens of tendon graft reveals an interesting course of events. Although the basic histologic process is the same in both the simple end-to-end suture and in the graft, the presence of a tendon graft in the defect is seen to play a definite rôle in healing.

*Fourth to Seventh Day.*—In a specimen removed on the fourth day after operation (fig. 4), the stumps and graft are united by the silk suture material over which there is proliferation of sheath tissues from each end, so that the gap is bridged across both by silk and living tissue. The sheath proliferation at this early stage is fibroblastic and is not yet sufficiently strong to take on the function of the tendon. The tendon

tissue in the graft is alive, but shows as yet no evidence of proliferation. There is some necrosis about the silk as it lies in the tendon, and there are irregular defects in the tissue. There is very little proliferation at this early stage about the intratendinous tissues of the graft. In the stumps, however (fig. 4 C), the intratendinous tissue (peritenonium internum) has proliferated, and at the place marked *x* in the illustration there is seen quite a wide strip of proliferating tissue which is pushing outward from between the tendon bundles into the intervening tissues toward the graft.

*Eighth Day.*—By the eighth day, the tendon stumps and graft are solidly fused together by thick strands of connective tissue (fig. 5), which make the newly reorganizing tendon look very thick and heavy. Important changes are taking place at this time. The stumps and graft are surrounded by sheets of tissue which can be separated from them only by sharp dissection. They appear to form an integral part of the new tendon at this stage.

The most important factor leading to union at this time is the sheath proliferation. In figure 6 A, which shows the proximal suture line at the seventh postoperative day, the distal end of the proximal stump is shown at *Pr. St.*, and the proliferated sheath at *Sh.* In the earlier stage, the thickened sheath was made up mainly of irregularly arranged fibroblasts; in this specimen the sheath tissue is beginning to arrange itself into long lines and bands of connective tissue fibers which run for considerable distances over the stumps and graft. This longitudinal arrangement is nicely shown in figure 6 C. At the suture lines, these connective tissue strips bridge across the defects and directly unite stumps and graft. The sheath proliferation and union are particularly striking if the sections pass through a silk knot lying between stump and graft, as is seen in figure 6. Here the defect presents itself as an actual absence of tissue, while to either side the thickened sheath insures union. Also where the stump and graft have separated, we find that the sheath tissues dip into the gap and play an important part in its organization (figs. 6 A and 7 A).

Changes begin to appear in the tendon tissue itself about the seventh day. Along with the proliferation about the intratendinous vessels, which has been noted in the earlier specimen, the tendon nuclei are beginning to increase in number. This increase is particularly marked in the ends of the stumps and the ends of the graft (figs. 6 A and 7 A). The closely approximated tips of the stumps and graft in a specimen stained with hematoxylin and eosin stand out as dark blue zones. From the ends of these zones, feather-like strands of cells push out into the intervening tissues. Throughout these zones and for a distance up and down throughout the tendon, there is noted a considerable increase in

the number of nuclei, which are becoming larger and more vesicular in character. Instead of the rod-shaped nuclei, which are seen in resting tendon (e. g., many of the nuclei in fig. 7 *B*), they are becoming more and more oval or even round and numerous mitoses are present, especially in the tips of the stumps (figs. 7 *C* and 8 *A*). It is especially interesting to note that the graft shows the same proliferative changes as the stumps. The central parts of the graft exhibit areas of necrosis that tend to become more numerous and of greater extent as the distal end of the graft is approached.

The intratendinous blood vessels, especially in the proximal stumps (fig. 7 *B*), are increased in number, and there is an increase in cells about them. At the ends of the tendon, the tissues from about these vessels send cords of cells into the intervening tissues (fig. 7 *A*).

There is considerable inflammatory infiltration in the sheath tissue as well as in the tendon itself.

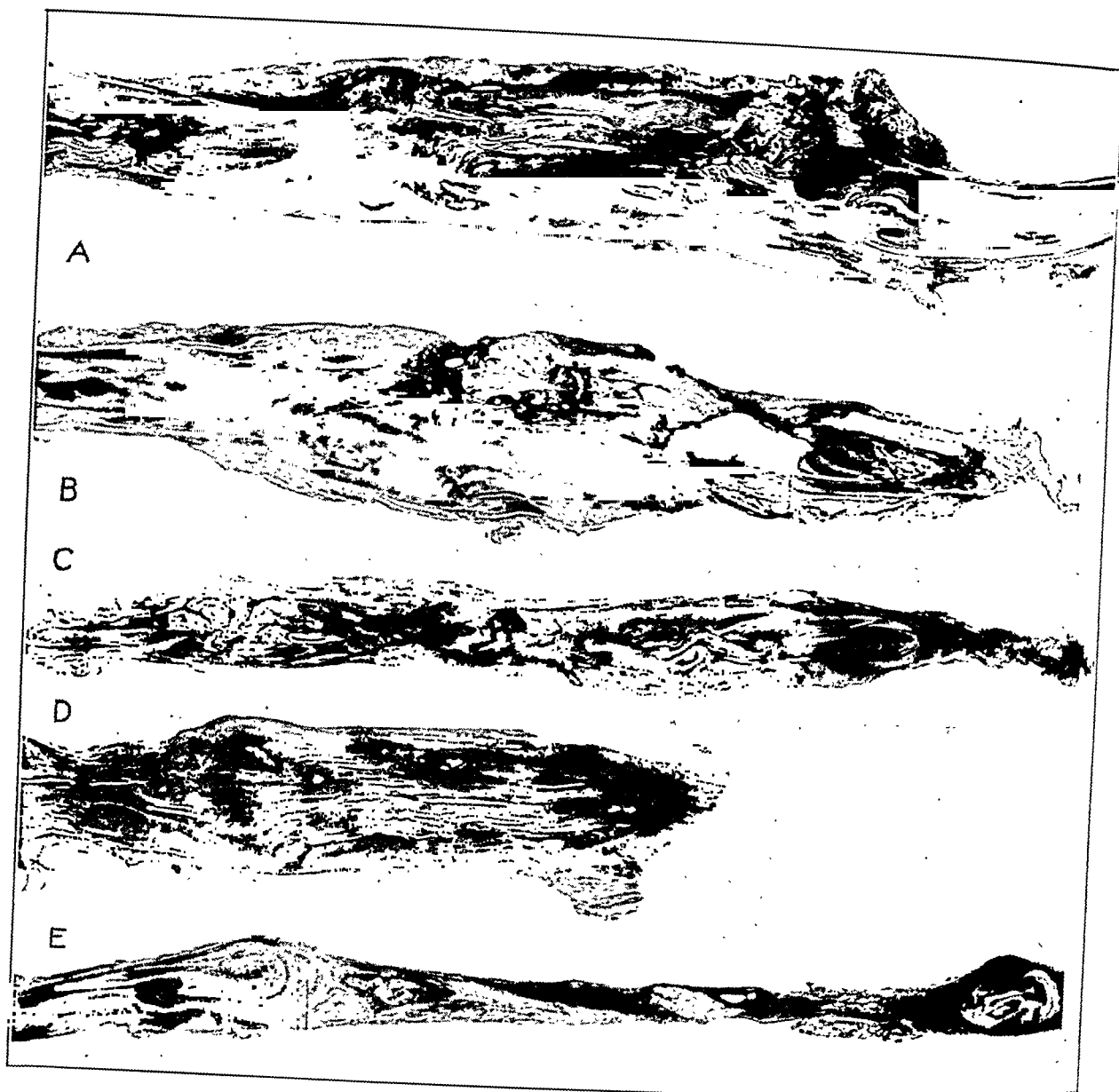
*Eighth to Tenth Day.*—From the eighth to the tenth day (figs. 9, 10, 11 and 12), the processes noted in their incipency are becoming more distinct. The tendon proliferation from the stumps, more particularly from the proximal stump, is progressively infiltrating the tissues lying between it and the graft (fig. 9 *C*). Long fibrils may be traced from the tendon into the intervening tissues, where they become lost in the organizing scar. The nuclei throughout the tendon of the stumps, especially in the ends and in irregular zones throughout its length are increased in number, and mitoses are frequent. The clefts between the separate tendon bundles at the ends of the stumps are widened by an increase of cells about the intratendinous vessels. From these clefts, bundles of cells push out and take part along with the tenoblasts in the formation of the scar. In the parts of the stump that contain the silk, considerable defects are seen (fig. 9 *A*). About the silk and in these defects is considerable inflammatory infiltration (fig. 9 *A* and *B*). Where silk suture material lies at the end of the stump (fig. 9 *B*), it forms a barrier to the infiltration of the tenoblasts, although the cells push out on all sides of and beyond the silk. As in the earlier stages, tendon necrosis about the silk and inflammatory infiltration in the tendon are seen. The effective union at this time is due to the sheath tissues (fig. 10) which are becoming definitely organized into dense connective tissue in which the fibers are arranged in long rows parallel to the line of tendon pull (fig. 10 *A*). The nuclei of the sheath are beginning to flatten out and assume the character of adult fibrous connective tissue nuclei. The tissues of the sheath are still very much permeated with white blood cells, which in many places (fig. 10 *A*) are accumulated into fairly large foci. In places where the pulling out of the silk has resulted in the production of large defects (fig. 10 *B*), the importance of sheath union is especially striking.

During the first eight to ten days, the tissues lying between the ends of the stumps and the graft (i. e., the intervening tissues) are not so well organized in some specimens as in others. Thus, when the samples of intervening tissues taken from three different specimens of approximately the same age are contrasted (fig. 11 *A*, *B* and *C*), it is seen that in one the whole area is little better than an abscess cavity or a hematoma (fig. 11 *A*), while in another there is seen the most delicate of beginning granulation tissue (fig. 11 *C*). In the central specimen of this group (fig. 11 *B*), the silk has so disrupted things that organization about it would be very slow and difficult. These only serve to emphasize again the importance of sheath union in the early stages. In contrast to these poorly developed areas of organization is the intervening tissue at the distal end of the proximal stump, as shown in figure 9 *C*; here the tissue is dense and strong and contains numerous tenoblasts from the proliferating stump.

It might be noted here that examination of numerous specimens at various stages shows an extremely varied histologic picture. It is very difficult to assign any day by day chronology to any series. It is only by the examination of a large number of sections that a chronologic picture can be established. A specimen of eight days may resemble one of five or ten days. In some, the proliferation of the tendon is marked, while in others the proliferation is very slight. In some, the graft remains almost entirely viable, while in others it becomes almost entirely necrotic. Far from being a discouraging factor, this varied nature of the findings only serve to accentuate the various parts of the healing process. Thus when the intervening tissues are poorly organized, the proliferative changes in the sheath are brought into the foreground.

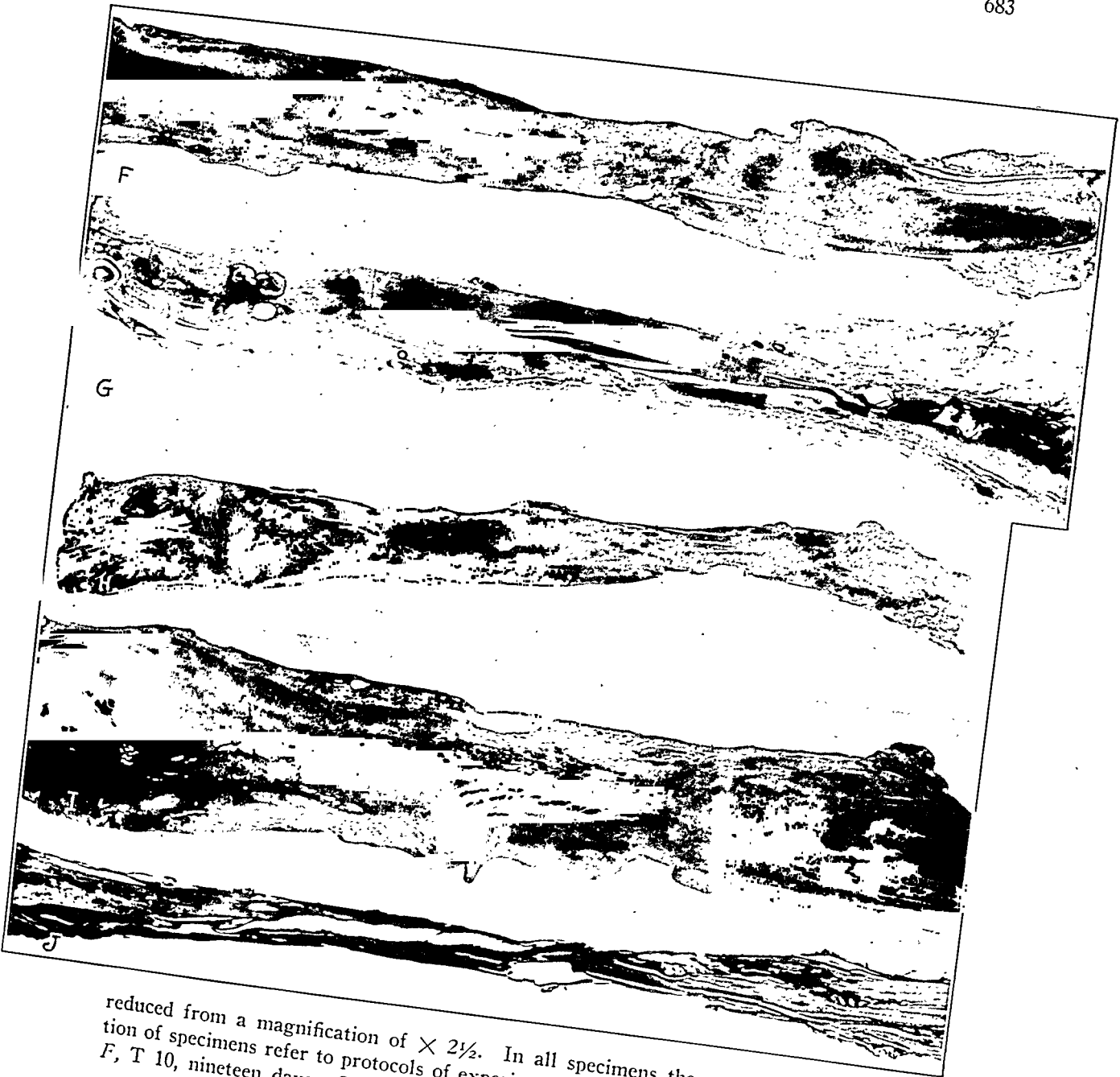
The graft may or may not be living during this eight to ten day period. There may be large areas of necrosis throughout (fig. 12 *A*, *B* and *C*), frequently infiltrated with leukocytes and certainly taking no part in the healing process. However, in other specimens, large areas of the graft are alive (fig. 12 *D*) and show evidence of proliferation. No very beautiful examples of tendon proliferation are found in these particular specimens, but this is apparently due to chance, since in the next group to be described, good proliferating graft can be seen.

*Twelfth to Fourteenth Day.*—In specimens removed from the twelfth to the fourteenth day, the proliferative changes seen in the stumps, especially in the proximal stump, have progressed. Throughout the stumps are seen a marked increase in tendon nuclei, an increase in number of the intratendinous blood vessels and of the cells of the endotenonium. The stumps, as a whole, are becoming more nuclear (fig. 13 *A* and *C*), and the longitudinal marking due to the intratendinous vessels is much more in evidence. From the ends of the stumps (figs. 13 *B* and 14 *A* and *B*), the proliferating tenoblasts push



Figs. 25 and 26.—Series of microscopic sections arranged in order of age; at the left, the graft in the center and the distal stump at the right. For description, see text. *C*, T 23, twelve days; *D*, T 22, fourteen days; *E*, T 2 R, fourteen days; *I*, T 13, twenty-five days; *J*, T 11, one hundred days.

outward for a considerable distance into the intervening tissues, and in places (fig. 14 *B*) where the gap between the stump and graft is not great, there is union between the tendon tissues by means of actual tenoblasts. Where the gap is greater (figs. 13 *B* and 14 *A*), the cords of proliferating tendon cells with their rather delicate stroma and large oval nuclei can be followed for long distances into the intervening



reduced from a magnification of  $\times 2\frac{1}{2}$ . In all specimens the proximal stump is sectioned at the same level. *A*, T 24, seven days; *B*, T 17, seven days; *C*, T 10, nineteen days; *D*, T 18, twenty-one days; *E*, T 1 L, twenty-two days; *F*, T 10, nineteen days; *G*, T 18, twenty-one days; *H*, T 1 L, twenty-two days; *I*, T 10, nineteen days; *J*, T 18, twenty-one days; *K*, T 1 L, twenty-two days.

In some instances (fig. 15 *B*), it is not possible with moderate magnification to locate the place at which the stump goes over into the intervening tissues.

The sheath tissues about the stumps and graft during this period are still very thick, strong and vascular (figs. 13 *A* and *B*, 15 *A* and 16 *A*). The sheath is still playing a very important rôle in the union,

but not nearly so important a rôle as in earlier specimens. It is much more adult in character, is dense and fibrous and arranged as long bands parallel to the course of the tendon.

The tissue intervening between the stumps and graft is beginning to assume adult character. In some favorable instances in which there has not been too much separation between the tendon ends, this gap has been filled in with a scar the origin of which is from (*a*) the proliferating sheath that dips into the gaps and helps organize them, (*b*) the proliferation of fibroblasts from the endotenonium at the ends of the stumps and graft and (*c*) from the infiltration of tenoblasts from the ends of the tendon. Although, macroscopically, the places at which tendon goes over into intervening tissue is often easily distinguished (fig. 25 of dog T 22 and fig. 26 of dog T 10), the distinction is not easily made under magnification. There is seen a transitional zone from tendon stump to intervening tissue (fig. 15 *B*) through which tenoblastic fibrils may be traced from the stump far into the tissues, or in case apposition is good, clear across the gap from stump to graft (fig. 14 *B*). The intervening tissue (fig. 15 *C*) is becoming arranged in longitudinal rows of cellular fibers; the nuclei are flattening out and are becoming arranged in a direction parallel to the pull of the forming tendon. The numerous blood vessels throughout the tendon scar show a beginning tendency to run in parallel longitudinal rows between the fiber bundles.

The changes noted in the stumps in the twelve to sixteen day specimens are also seen in the graft, though in not quite so advanced a stage (fig. 16). The proximal end of a twelve day graft shows the same budding of tenoblasts (fig. 16 *C*) as was seen in the stumps. In places in which apposition has been good, these bundles may be traced across the gap (fig. 14 *B*) to mingle with the tenoblasts from the stumps. The nuclei throughout the graft are becoming more numerous (fig. 16), oval or round in shape and vesicular. This nuclear increase tends to occur in areas of oval zones or longitudinal strips (fig. 16 *B*), as was noted in the stumps. Along with the nuclear increase, the tendon fibrils tend to lose their wavy course and to form long straight bands of fibers, as seen in figure 16 *A*, in which tendon fibers of the graft along the lower edge of the section are still wavy, while those in the upper part were flattened.

A specimen removed at fourteen days (from dog T 29) and tested rather crudely for strength broke with  $11\frac{1}{2}$  pounds pull through the proximal intervening tissue, which, while fairly well organized, was not yet capable of function. The sheath union is still the stronger, though its importance is not so great as in the earlier specimens.

*Third Week.*—During the third week, the organizing tendon is beginning to show a certain uniformity of structure (fig. 17). It is still possible to distinguish the stumps, the graft and the intervening

tissues, but they are behaving as a whole, and are becoming organized into dense fibrous-like strands. The stumps show resting tendon tissue in but a few areas and these at a distance from the suture line. Most of the stump (fig. 17 *A* and *D*) is made up of closely packed fibers arranged in longitudinal strands with longitudinally placed blood vessels running between them. The nuclei in these strands are very numerous and are flattening out; many are quite flattened (fig. 18), though the oval forms noted in the earlier specimens have not entirely disappeared. The intervening tissues (fig. 17 *C*) and the graft (fig. 17 *B*) are also made up of solidly packed fibers. In the region of the graft, one can occasionally make out small stretches of deeply eosin-stained adult tendon, but the majority has been converted into the same type of cellular tissue as was noted in the stumps. The sheath is no longer the important uniting structure that it had been previously. It is still thickened, but is beginning to loosen up and is more easily separated from the tendon. It is assuming the important function of serving as gliding tissue for the new tendon.

*Fourth to Fifth Week.*—During the fourth and fifth weeks, the tendon attains great strength, owing to the further development of the tissues coming from the stumps and graft. The stumps and area between them become narrower and more condensed. The newly formed tendon (fig. 19 *C*) is covered over by loose sheets of new sheath tissue, which allow it to glide freely. Tendons at this stage will sustain a pull of from 36 to 40 pounds before rupturing. In two instances (figs. 19 *B* and *C* of dog T 31 and *C* and *D* of Dog T 27), the break occurred at the distal suture line; in one instance (fig. 19 *A* of dog T 28), the rupture took place at the proximal suture line with a pull of slightly over 40 pounds.

The microscopic changes during the fourth and fifth weeks (fig. 20) are a progression of those observed in the third week. The tissue is becoming more and more compact and is taking on more and more uniformity in structure throughout the whole reorganizing tendon. It is considerably more nuclear than adult tendon, but is not ordinary scar tissue. The stumps (figs. 20 *A* and 21 *A* and *B*) are not so thick and nodular as in earlier specimens. They are made up of parallel rows of dense cellular bands between which run longitudinally arranged blood vessels more numerous than in normal tendon. The nuclei are mainly flattened and arranged in rows parallel to the course of the fibers. Here and there one still sees accumulations of round cells about the vessels (fig. 20 *A* and *C*) or about bits of silk. Even in the parts of the stumps in which the suture has led to great disruption of tendon fibers, the tissues about the disrupted areas are well organized, and in the specimen illustrated (fig. 21 *B*), the stumps withstood a pull of 35 pounds before rupture took place through another part of the new tendon.



A comparison of tissue taken from the region of the graft and from the tissues that unite graft and stumps (fig. 21 *B* and *C*) show that the whole stretch is made up histologically about the same as the stump, in fact, selected places from these different areas (fig. 20) are practically indistinguishable.

*One Hundred Days.*—A single dog was allowed to live one hundred days before being killed (fig. 22). The dog had never worn a cast, but had been allowed free full use of the leg immediately after the operation. He had excellent functional use of the leg (fig. 22). In this specimen, we have the further progression of the condensation noted in the tendon removed four to five weeks after operation. The silk through the central parts (fig. 26) was pulled out during sectioning, leaving long defects in the new tendon. It is not possible, microscopically, to determine the limits of stumps or graft. The stumps can be distinguished because they are somewhat wider than the tissue between them, but on microscopic examination (fig. 23 *A* and *B* and fig. 24 *A*), it is seen that they and the thinner tissues between them (fig. 24 *B*) have the same histologic characteristics. The tissues are assuming more and more the appearance of normal tendon, though they can still be easily distinguished from it. The fibers are flattened out into long rows parallel to the line of pull, and the nuclei, much reduced in number in comparison to earlier specimens, are flattened and rod-like and also arranged in parallel rows.

#### RÉSUMÉ OF HEALING PROCESS OF TENDON GRAFTS

In brief résumé, the process of healing of a tendon graft may be divided into two phases. During the first phase, which may be assigned to the first two weeks, the union between graft and stumps is effected by proliferation of the respective sheaths or peritendinous tissues. This phase represents the period during which the tendon is becoming more vascularized and is itself beginning to proliferate. The second overlaps the first and is the phase of tenoblastic proliferation. It begins about the fourth or fifth day after operation, i. e., at the time the first tendon mitoses are apparent. The effectiveness of the union due to the tendon participation depends on the amount of separation between the tendon and graft. Usually by the end of the second week the process is well under way and small defects are already bridged across by tenoblasts. From the second week on, the second phase becomes the most important, so that the new tendon is formed essentially from the organization of a scar that lies between the ends of the graft and stumps and in the formation of which the tenoblasts themselves play the most important part. As the importance of the sheath as a uniting structure diminishes, it begins to take up the important function of serving as gliding tissue. During the fourth and fifth

postoperative weeks, the sheath becomes progressively more easily separated from the organizing tendon, and with successful union there results a well organized tendon with a paratendon arrangement about it. A new synovial sheath has not been observed to form during the period of these experiments.

#### COMMENT ON RESULTS OF EXPERIMENTAL WORK

The process of healing of tendon wounds is seen to be dependent on a number of different factors that are mutually interactive and that are all essential to a proper reestablishment of functional continuity. It is believed that in the surgical repair of injured tendons a knowledge of the histologic process of repair should result in an improvement of results in this difficult field. It is believed also that with this knowledge as a background, further experimental work can be done with profit.

#### THE IMPORTANCE OF THE SHEATH AND PERITENDINOUS TISSUES

The connective tissues surrounding the tendon, with the exception of the dense osteofibrous tunnels, are of the greatest importance in the repair of a tendon wound. They have the most intimate relation to the tendon, convey blood vessels and lymphatics to it, and permit easy gliding of the tendon. In the case of such tendons as the extensors on the dorsum of the hand or foot, as the achilles tendon and a few other paratenon covered tendons, the sheath tissues can provide for spontaneous repair, albeit often in a lengthened condition. Even where the sheath tissues are scanty, as, for example, in the synovial covered tendons, they are also important, but, depending on their amount, are less efficient than paratenon. For example, in the wrist the tendons are covered by a synovial sheath, and are provided with a rather large and continuous mesotenon that brings blood vessels and lymphatics to the tendons. Because of the number of tendons enclosed in one synovial layer, there is a good deal of connective tissue associated with the mesotenon and lying between the various reflections of the synovial sheet. While spontaneous repair at the wrist does not take place, operative repair, if correctly done, has a fairly good prognosis. The flexor tendons throughout their course on the fingers, however, have very scanty synovial sheaths. The visceral layer of the synovial sheath lies directly on the surface of the tendon, with very little, if any, connective tissue below it, and the parietal layer is likewise closely applied to the inner surface of the osteofibrous canal. The mesotenons of these tendons are reduced to tiny bridges, the vincula, which carry tiny blood vessels, possess little connective tissue and tear away from the tendon if any great pull is put on them. In tendons of this type, it is obvious that the sheath would be of little value in repair, and that here other methods of suture or surgical repair would have to be applied than in the case of tendons on the dorsum of the hand or in

the wrist. In the comment on tendon repair that follows, the tendons on the volar surface of the fingers, enclosed in synovial sheaths with osteofibrous tunnels, are not included.

As soon as a defect in a tendon results, the tendon ends retract a variable distance, and the sheath tissues fall at once into the resulting gap. If the defect has been sutured, a similar though usually smaller gap frequently occurs, and we have found it always to occur experimentally. Under favorable circumstances, the sheath begins to proliferate shortly after the injury, and by the end of four or five days has produced a bridge of fibroblastic material which encloses both stumps and tends to prevent or at least to minimize further separation. This first callus, like callus on a fractured bone, produces a nodular swelling at the site of injury. During the next two weeks this fibrous bridge forms the more important and at times, if the gap is too great, the only union between the stumps. If the gap is not too great, the tendon proliferation will be able to bridge it successfully in two or three weeks under the protective splinting of the sheath. If too great a gap exists, a union of a sort takes place which is mainly connective tissue and is liable to further stretching.

After the sheath serves its initial function of uniting the stumps, the outer layers loosen up and again take over the function of serving as gliding tissue for the tendon.

It is important, then, in suture of a divided tendon that the sheath tissues be as carefully handled and preserved as the tendon itself. The greatest care should be exercised to avoid stripping this tissue from the tendon. Transverse division of this tissue should be avoided, or, if the sheath is already divided transversely, it should be repaired. If possible, sheath tissues of one stump should be united with as little trauma as possible to similar tissues of the other stump. In operating on enclosed tendons in the synovial sheath, the mesotenon should not be disturbed, but should be left attached to the tendon even though suture is more difficult.

In the case of tendon graft the sheath tissues are seen to take an important part in healing, comparable to that in repair by suture. The first tissues of a graft to show signs of proliferation and to effect union are the connective tissues surrounding it. As in the case of suture, the gaps at either end of the graft are first bridged across by connective tissue resulting from the proliferation of the sheaths about the stumps and graft. This union serves to splint the graft in place until the tendons can directly unite by tendon cell proliferation.

Therefore, in performing a tendon graft, the graft should be left surrounded by its own, carefully handled and preserved, peritendinous tissues. These tissues should be united to similar tissues about the stumps.

## THE TENDON

We believe that these studies have shown that the tendon itself takes an important part in healing, but that, because of its scanty blood supply and the very nature of its tissue, it begins its proliferation late and that it progresses more slowly than ordinary connective tissue. This tardiness of tendon response is compensated, however, by the early response of the sheath.

To take advantage of tendon proliferation, one must carefully avoid traumatizing the tendon, and especially must one avoid injury to the ends of the tendon that one wishes to bring together. These studies have shown that the tendon ends start to proliferate about the fourth or fifth day after suture and to send out bands of cells and fibrils into the gap tissue beyond. If the tendon is injured, or if it is stripped of blood supply, necrosis is likely to occur and delay the process.

This consideration of avoidance of injury of the end of the tendon leads one to doubt the wisdom of sutures that pass through the end of a tendon and lead to the disruption of its fibers. Certainly the wisdom of placing knots between the ends of united tendons is doubtful. Microscopic sections show that these cause a very definite barrier between the tendon ends and prevent, for a considerable time, the ingrowth of tendon fibers into the gap.

A tendon suture, it seems to us, should combine two properties, first that of preventing or minimizing retraction and that of obtaining a good end-to-end apposition. The first of the requisites may be met by the use of a tension suture that has a secure hold on the tendon and will not split through it. The points of attachment of the suture to the tendon should be 1 cm. or more from the end of the stump so as to leave this untraumatized. It should be tied so that the knot does not lie between the tendon ends. The second of these properties is met by an appositional suture, which should be of very fine material and threaded on very fine needles. It should be passed through the tendon end in such a manner as to traumatize it as little as possible. It may be placed through sheath tissues, as is done in suturing nerves, or it may pass through the very periphery of the tendon. A single fine suture passed first through one stump and then through the other and tied outside may be enough to maintain apposition. Experimental work now in progress with this type of suture has given promising results, as have also several clinical cases. The presence of the silk on the outside of the tendon does not apparently interfere with function, while the absence of a knot between the ends is an advantage.

*Retraction.*—Retraction has always occurred despite careful and satisfactory suture and efficient splinting. Whether this is true in surgical intervention on human beings we cannot say, but we may reasonably assume that it is. Since it is necessary that the gap be

bridged across by tendon, it is evident that the wider the gap, the greater the distance the tendon fibrils and cells must penetrate and the greater chance there is for scar tissue to interfere. It may be wise in performing end-to-end suture of tendon in instances in which tension is considerable to put in a small segment of tendon graft. It has been shown that under favorable circumstances the graft remains viable and proliferates and unites with either stump at the ends of the defect. In this manner a tendon-to-tendon union is more quickly obtained.

*Tendon Grafts.*—These experiments have shown that tendon with its surrounding connective tissue maintains its vitality when transplanted as a free graft. The sheath very soon fuses with the sheath tissues of the two stumps, the tendon itself remains alive and soon proliferates and fuses with the stumps. In this manner actual tendon tissue bridges the defect. Although many surgeons have advocated the use of fascia or other connective tissues for tendon grafts, their position does not seem logical. A fascial tendon or a tendon formed about silk is after all scar tissue, and as such has all the defects of scar tissue—the danger of contracting or of stretching.

#### SUMMARY

The process of healing of tendon wounds and the manner in which injuries of tendons are repaired following suture or graft have been and still are a matter of considerable controversy. The most controversial question has been the source of the material which forms the tendon callus, and it appears from a study of the literature that investigators have in the main attempted to show that either the tendon itself played the major rôle in healing or that the connective tissues associated with the tendon were the important sources of material. In the present experimental study carried out on the extensor carpi radialis tendon of the dog, an attempt has been made not only to ascertain the source of tendon callus, but to evaluate the parts taken by the various tissues concerned. It is shown by histologic study of healing tendon sutures that union is effected first by proliferation of the sheath tissues. This union serves to reestablish continuity in a few days. After the fourth or fifth day the tendon itself begins to proliferate and to send cells into the callus, and, if the gap is not too great, it may be bridged by tendon cells in about two weeks. After the sheath has served its purpose of splinting the first union, it begins to become more lax and areolar and in a successful suture to take on again its original function of serving as gliding tissue. In the experiments with autogenous tendon grafts, a process of healing similar to that of sutured tendons was found to take place. The only variation between the two processes was that the sheath of the graft and the tendon of the graft remained viable and took part in the bridging of the gap between the

separated stumps. From these experiments it would appear that the following practical conclusions can be drawn:

1. In tendon suture the sheath tissues, if any are present, should be as carefully approximated as the tendon, since they afford an early union which functions while the tendon itself is proliferating.
2. Accurate end-to-end apposition of tendon stumps is beneficial to healing.
3. Movements of sutured tendons may be started cautiously by the fifth or sixth day, but no force should be exerted before the third week.
4. Defects in tendons should be filled with a tendon graft plus its sheath tissues and not by fascia, since the tendon graft forms true tendon which will not tend to stretch as would ordinary connective tissue.

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## TRAUMATIC SHOCK

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The current theories as to the initiation of traumatic shock have been reviewed so often and so well<sup>1</sup> that it will not be necessary to repeat them. In 1919, Cannon and Bayliss<sup>2</sup> traumatized the thigh muscles of cats and other animals, thus producing a prolonged lowering in the blood pressure, which they ascribed to a toxin originating in the traumatized area. Since that time, the toxic theory of traumatic shock has become widely accepted. The actual experiments reported were few, and the data were scanty. The original theory was based largely on the analogy to shock produced by histamine. Since that time many others have worked on the problem, with the result that there has been practically no positive evidence of toxemia, while there has been considerable direct negative evidence. The argument for toxemia rests largely on the presumptive exclusion of other factors, the chief of which are the nervous system and hemorrhage. The question remains as to whether the nervous system and hemorrhage were completely excluded in the experiments of Cannon and Bayliss. More recent workers, particularly Parsons and Phemister<sup>3</sup> and Blalock with his

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1. Cannon: *Traumatic Shock*, New York, D. Appleton & Company, 1923. Blalock, Alfred: *Experimental Shock: The Cause of the Low Blood Pressure Produced by Muscle Injury*. *Arch. Surg.* **20**:959 (June) 1930. Smith, M. I.: *Studies on Experimental Shock with Especial Reference to Its Treatment*, *J. Pharmacol. & Exper. Therap.* **32**:465 (April) 1928.

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associates,<sup>4</sup> have offered proof that hemorrhage together with local fluid loss in the traumatized area can explain all the phenomena. However, even in their experiments it is questionable whether the nervous system had been completely excluded. There are other objections which will be offered later. The two factors, nervous system and hemorrhage, will be discussed separately.

Since the majority of the experiments were on trauma as applied to the muscles of a posterior extremity, the nervous system was excluded by so-called denervating the limb or cutting the spinal cord in the lower dorsal region. In many instances it is not stated specifically what is meant by a denervated limb. For example, the complete peripheral denervation of the thigh in a cat, so that no possible sensory impulses can travel to the central nervous system, involves the severance of at least eight nerves:<sup>5</sup> the femoral, sciatic, obturator, genitofemoral, lateral femoral cutaneous, posterior femoral cutaneous, superior gluteal and inferior gluteal. In addition, an arterial sympathectomy must be done. This could hardly be accomplished as an acute experiment, since the trauma of the operative procedure alone might cause sufficient shock to lower the blood pressure to a shock level. Even when the spinal cord is cut in the lower dorsal region, impulses could still travel up the sympathetic chain to a level above the point of severance. A spinal section cannot be done as an acute experiment without confusing the cause of the fall of blood pressure. In addition to cutting the cord, there is a sympathetic chain on that side that must be partly removed. Since in most of the previous experiments pretending to exclude nervous impulses either the cord alone or only the femoral and sciatic nerves were cut, we must conclude that while the experiments are suggestive that nervous impulses do not initiate traumatic shock, this has not been proved conclusively.

To exclude hemorrhage as the initiating factor is also very difficult. All trauma is accompanied by hemorrhage, and there are no exact

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methods for accurately measuring the amount. Cannon and Bayliss weighed both the traumatized and untraumatized limbs in cats and took the difference in weight as representing the loss of blood. They concluded, without reported control bleeding experiments, that the loss was not sufficient to account for the fall in blood pressure. Furthermore, they amputated the limb in the upper region of the thigh, so that it is questionable whether they were entirely above the area of extravasation. Parsons and Phemister, and also Blalock, working with dogs, used many more animals than Cannon and Bayliss but came to opposite conclusions. They stated definitely that the loss of blood being over 40 per cent of the estimated blood volume, it was sufficient to account for the shock. The objection to the latter groups of experiments is that the amount of trauma applied was not constant in the various experiments. Trauma was continued at frequent intervals until the blood pressure fell to the desired level. Obviously one can traumatize an animal enough to cause a fatal hemorrhage. The important point would be to see with how little hemorrhage shock could be produced by trauma, and the period of trauma should be very brief if it is to correspond with clinical phenomena. After determining the loss of blood in traumatized animals, other animals of comparable weight should be bled the same amount in practically the same length of time in order to observe whether the blood pressure curve, clinical symptoms and end-results are the same as those following trauma.

The question of whether the blood is actually concentrated in traumatic shock should be settled more definitely so that it can be determined whether this is a reliable sign in differentiating shock from hemorrhage. The evidence on this point is so conflicting that it is impossible to reach any conclusions. The anesthetic effects and the duration of the experiments are important factors.

The experiments reported here were planned to obviate these objections. The purpose was (1) to establish a control series in which a definite brief trauma, not repeated, would cause a permanent fall in blood pressure with symptoms analogous to those of clinical shock, (2) to exclude the nervous system completely, (3) to measure the amount of blood lost in the traumatized area, (4) to bleed animals of comparable weight the same amount in a brief period and to compare this with the effects of trauma and (5) to determine from hemoglobin estimation of the arterial blood whether there was concentration or not.

#### CONTROL EXPERIMENTS

*Method.*—Cats weighing from 2 to 4 Kg. were anesthetized by the intramuscular injection of sodium barbital, 0.3 Gm. per kilogram of body weight. A cannula was inserted in the carotid artery. Trauma was produced by striking the inner aspect of one thigh one hundred and fifty rapid blows with a wooden mallet. This

was always done by the same person so that the strength of the blows was fairly constant. The whole period of trauma was less than five minutes. Blood for hemoglobin determination was drawn from the exposed brachial artery before and at intervals after the trauma.

In previous experiments it was found impossible in dogs to produce constantly a typical picture of shock by traumatizing the muscles for a single brief period. However, in cats weighing less than 4 Kg., one hundred and fifty rapid blows to the thigh with a wooden mallet during the period of about three minutes practically

TABLE 1.—*Results in Control Experiments Following Trauma*

Number	Weight, Kg.	Initial Blood Pressure, Mm.	Final Blood Pressure, Mm.	Time	Relative Hemoglobin, per Cent*	Relative Solids, per Cent
1	2.69	144	56	4 hrs. 5 min.	82	..
2	2.91	115	62	3 hrs. 10 min.	79	..
3	2.75	138	Died	8 min.	..	..
4	2.35	148	Died	15 min.	..	..
5	3.015	150	Died	14 min.	..	..
6	3.085	175	76	4 hrs.	85	..
7	2.015	159	Died	1 hr. 32 min.	73	..
8	2.94	162	50	2 hrs. 30 min.	79	..
9	2.690	144	58	4 hrs. 5 min.	82	..
10	2.7	164	52	3 hrs. 50 min.	81	..
11	2.850	162	Died	2 hrs. 50 min.	63	..
12	2.5	145	80	3 hrs. 30 min.	92	..
13	3.3	160	55	3 hrs.	80	..
14	2.563	152	115	3 hrs. 40 min.	91	..
15	2.47	130	80	3 hrs. 50 min.	86	..
16	2.77	120	63	3 hrs. 5 min.	92	..
17	2.615	152	50	3 hrs. 10 min.	78	..
18	2.0	160	Died	2 hrs. 55 min.	84	53
19	4.0	160	Died	3 hrs. 25 min.	85	..
20	2.8	170	92	1 hr. 45 min.	..	80
21	2.5	170	60	1 hr. 25 min.	76	..
22	3.4	180	120	2 hrs. 20 min.	100	59
23	3.6	140	108	2 hrs. 55 min.	..	..
24	2.2	148	52	3 hrs. 5 min.	90	92
25	1.9	140	78	3 hrs. 25 min.	..	..
26	2.2	150	100	2 hrs. 55 min.	88	90
27	2.7	160	Died	1 hr. 45 min.	..	..
28	2.3	180	80	1 hr. 50 min.	98	98
29	1.9	156	80	2 hrs. 5 min.	..	..
30	3.25	160	Died	2 hrs.	83	82
31	2.5	162	Died	50 min.	75	87
32	3.05	170	114	3 hrs.	93	93
33	2.1	150	82	1 hr. 40 min.	..	..
34	2.6	160	62	2 hrs.	..	..
35	3.5	180	70	1 hr. 25 min.	..	..
36	3.0	130	78	1 hr. 55 min.	96	99
37	1.95	152	88	1 hr. 40 min.	76	74
38	2.6	150	Died	2 hrs. 5 min.	86	85
39	2.45	170	Died	2 hrs. 30 min.	93	..
40	2.94	184	Died	2 hrs. 15 min.	..	..

\* First determination of hemoglobin and solids on the blood drawn before trauma is taken as 100 per cent.

always produced a typical blood pressure curve with the clinical picture of shock. Nothing was done to the animals after the trauma except to record the blood pressure every five minutes and to take small samples of blood from the brachial artery for hemoglobin determinations.

*Results.*—Forty animals were used as controls (tables 1 and 2). Thirteen died in periods varying from eight minutes to three and one-half hours following trauma. The average time from trauma to death was one hour and forty-five minutes. Twenty animals had a blood pressure of 80 mm. of mercury or below at the end of the experiment.

which lasted from one and one-half to four hours after the trauma, with an average of two hours and fifty minutes. Only seven animals had a blood pressure of over 80 mm. in experiments lasting from one hour and forty minutes to three hours and forty minutes. In three of these the blood pressure was below 100.

**Blood Pressure:** The blood pressure curve following trauma was constant (fig. 1). There was a sharp rapid fall of from 50 to 100 mm. of mercury beginning about the middle of the trauma and more pronounced toward the end. In some instances the fall would continue a few seconds after the trauma. More often, however, it was beginning to rise before the trauma was ended. There was a rapid recovery of about half of the fall within a few minutes and a slower recovery, lasting from fifteen to thirty minutes, to within 20 or 30 mm. of the initial blood pressure. Following this, there was a slow fall to a level of 80 mm.

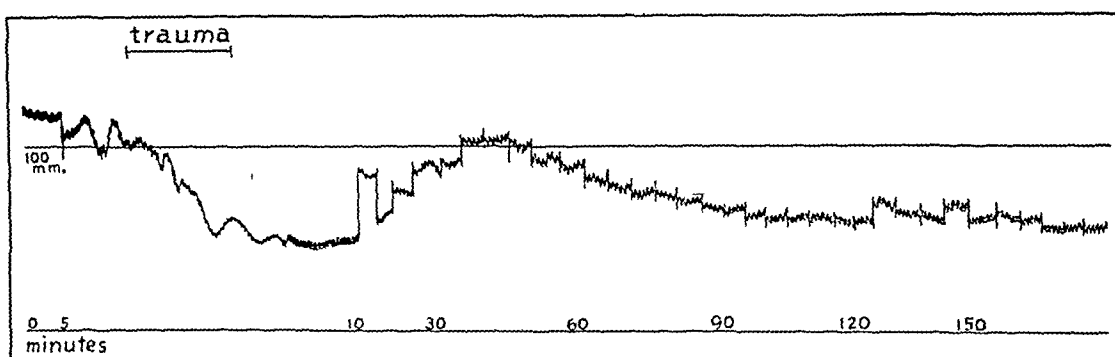


Fig. 1.—Blood pressure curve of a traumatized female cat (weight 3 Kg.) anesthetized with sodium barbital. At  $x-x$ , the left thigh was struck one hundred and fifty times.

or below in most of the experiments, which continued indefinitely with almost no tendency to recovery. In a few experiments the blood pressure kept falling rapidly until death occurred, with no tendency to recovery following the trauma.

In order to ascertain the effect of the dosage of barbital on the blood pressure curve, seven experiments were done in the manner previously described but with the trauma omitted (table 3). The cats weighed from 2 to 4 Kg., and the duration of the experiments was two and one-half to three and one-half hours. While occasionally there were variations in the blood pressure, the curve did not resemble that following trauma, and at the end of the experiment the blood pressure was about the same as at the beginning.

**Pulse and Respiration:** There was no characteristic change in the pulse rate except that when the pressure dropped to below 50 mm., the pulse suddenly became very slow, then after the pressure rose the rate

suddenly jumped back to the original speed or higher. As the experiment progressed the pulse rate remained very close to the original rate. Sometimes it was slower and sometimes slightly more rapid.

The respiration became more rapid and irregular during the period of trauma but soon settled down to a rhythm more rapid and shallower than at the beginning.

The foregoing experiments showed that in small cats a single brief interval of trauma applied to the muscles of one of the posterior extremities could constantly produce a condition simulating clinical shock with a constant typical blood pressure curve. This curve consisted of primary shock with recovery, a latent period, and then sec-

TABLE 2.—*Summary of Table 1*

Number of Animals	Died	Blood Pressure Below 80 Mm.	Blood Pressure Above 80 Mm.	Average Hemoglobin Reduction*	Average Solid Reduction†
40	13	20	7	15%	11.4%

\* Twenty-eight animals.

† Twelve animals.

TABLE 3.—*Results in Control Experiments Without Trauma*

Number	Weight, Kg.	Initial Blood Pressure, Mm.	Final Blood Pressure, Mm.	Time	Hemoglobin, per Cent of Change
1	2.7	170	120	2 hrs. 40 min.	...
2	1.9	124	120	2 hrs. 45 min.	...
3	...	155	125	2 hrs. 40 min.	...
4	2.46	130	120	3 hrs. 30 min.	-2
5	2.35	160	160	3 hrs. 20 min.	0
6	2.29	130	120	3 hrs. 30 min.	+1
7	2.67	140	134	3 hrs. 30 min.	-3

ondary shock, thus offering the same picture as was developed clinically during the Word War. The remarkable constancy of this blood pressure curve with the four definite divisions, a sharp rapid fall during trauma, rapid partial recovery, maintenance of a level for a brief period and secondary fall, gave a characteristic control curve for comparison in the following experiments.

#### EXCLUSION OF THE NERVOUS SYSTEM

The complete exclusion of the nervous connections of the limb can be accomplished by (1) cutting all the peripheral nerves, removal of the lumbar sympathetic chain and arterial sympathectomy; (2) cutting the spinal cord in the lower dorsal region in addition to the removal of the lumbar sympathetic chain and arterial sympathectomy, or to be absolutely sure, (3) the combination of cutting the cord, nerve section, lumbar sympathectomy and arterial sympathectomy. Any of the fore-

going procedures involve considerable operative trauma, hardly leaving the animal in a fit condition for an immediate experiment on traumatic shock. Therefore, it was necessary to do the nerve operations in stages as recovery experiments. For the first stage, the peripheral nerves and the sympathetic chain were severed, and a week or ten days later the lower dorsal cord was cut. These operations were done with aseptic precautions under ether anesthesia. From four to seven days following the section of the cord, with the animals in good condition, the shock experiments were done under sodium barbital anesthesia. Eleven animals were used. In four the cord alone was cut, in five the cord was cut, the bilateral lumbar sympathetic chain was removed and the iliac artery was stripped of its sheath, and in three the cord was cut in addition to the nerves, the lumbar sympathetic chain was removed and the iliac artery was stripped.

TABLE 4.—*Results in Nerve Experiments*

No.	Operation	Initial Blood Pressure, Mm.	Final Blood Pressure, Mm.	Time
1	Cord cut.....	142	Died	55 min.
2	Cord cut.....	130	80	2 hrs. 45 min.
3	Cord cut.....	140	Died	45 min.
4	Cord cut.....	110	62	1 hr. 50 min.
5	Cord cut with .....	156	80	2 hrs. 25 min.
6	Cord cut with .....	120	118	2 hrs. 5 min.
7	Cord cut with .....	130	60	2 hrs. 25 min.
8	Cord cut with sympathetic.....	120	64	1 hr. 25 min.
9	Cord cut with sympathetic.....	114	Died	1 hr. 15 min.
10	Cord cut, sympathectomy, nerves cut..	144	96	1 hr. 45 min.
11	Cord cut, sympathectomy, nerves cut..	120	76	1 hr. 40 min.

*Results.*—The results (table 4) were essentially similar to those in the control experiments. Three animals died in an average of eighty minutes, six had a blood pressure of 80 or below in average time of two hours and five minutes and two had a blood pressure of over 80 in average time of one hour and fifty-five minutes. The conformation of the blood pressure curve (fig. 2) did not differ from that of the controls. We can conclude, therefore, that the nervous system does not play an important rôle in the production of low blood pressure following trauma.

#### HEMORRHAGE

The problems involved in determining the rôle of hemorrhage following trauma are (1) to develop a relatively accurate method of determining the amount of hemorrhage in the traumatized area; (2) to bleed animals this amount of blood in a comparable length of time and compare the blood pressure curve with that following trauma.

*Method.*—At the end of the trauma experiments, both posterior extremities, the traumatized and untraumatized, were amputated at the sacro-iliac joint, the

iliac bone thus being included in order to get well above the area of extravasated blood. The muscles and skin of each leg separately were macerated in a grinder and put in a large amount of distilled water and allowed to stand overnight. The water was changed until the tissues were completely bleached. After filtration, a 10 cc. sample of the pooled washing of each leg was treated with 0.1 cc. of concentrated hydrochloric acid and read in a colorimeter against the Newcomer standard for hemoglobin concentration. The standard had been checked for oxygen capacity. Since the total amount of washings were known, this determination gave the total number of milligrams of hemoglobin in each leg. The difference gave the amount of blood lost in milligrams of hemoglobin.

At the beginning of the experiments and just before the end, blood samples were taken from the brachial artery for hemoglobin determination. The first sample gave the number of milligrams of hemoglobin per hundred cubic centimeters of blood. Since the total number of milligrams of hemoglobin lost was known, the number of cubic centimeters of blood lost could be determined.

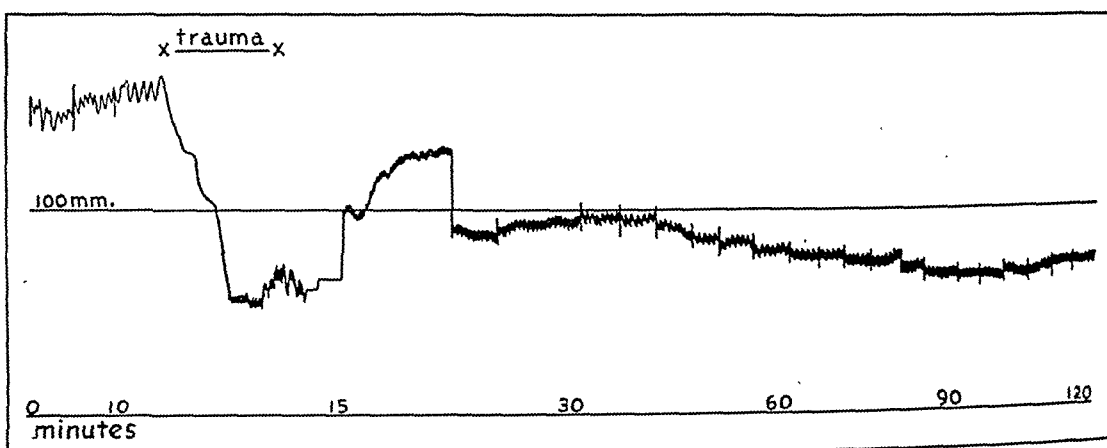


Fig. 2.—Blood pressure curve of a traumatized cat (weight, 2.4 Kg.) anesthetized with sodium barbital. The bilateral lumbar sympathetic chain was removed, and the left iliac arterial sympathectomy done eight days before. The spinal cord was cut in the lower dorsal region two days before. At  $x-x$ , the left thigh was struck one hundred and fifty times.

To check this method, a measured amount of blood was added to macerated muscle and then extracted as previously described. The result (table 5) showed that the error was less than 1 cc. in six experiments, 3 cc. in one, 4 cc. in one and 7.8 cc. in one. The average error was 1.9 cc., which in animals of the weight used would equal about 1 per cent of the blood volume.

To compare the effects of bleeding without trauma, cats of similar weight were bled by needle and syringe rapidly from the exposed femoral artery to the amount equal to the determined loss of blood following trauma. The bleeding time was five minutes or less, thus comparable to the time of trauma and the artery was clamped after the hemorrhage. Rapid bleeding was adopted because it was found that in following trauma, if the vessels were tied immediately, the blood pressure curve was not altered. Therefore, it was the acute bleeding which was the most important factor.

*Results.*—In comparing the effects of hemorrhage and trauma with equal loss of blood, one is struck by the similarity of the blood pressure

curves (compare figure 3 with figure 4, and figure 5 with figure 6). After hemorrhage there was the same immediate sharp fall with a rapid recovery and a latent period followed by the same slow fall to a low level which was frequently maintained. The general clinical picture

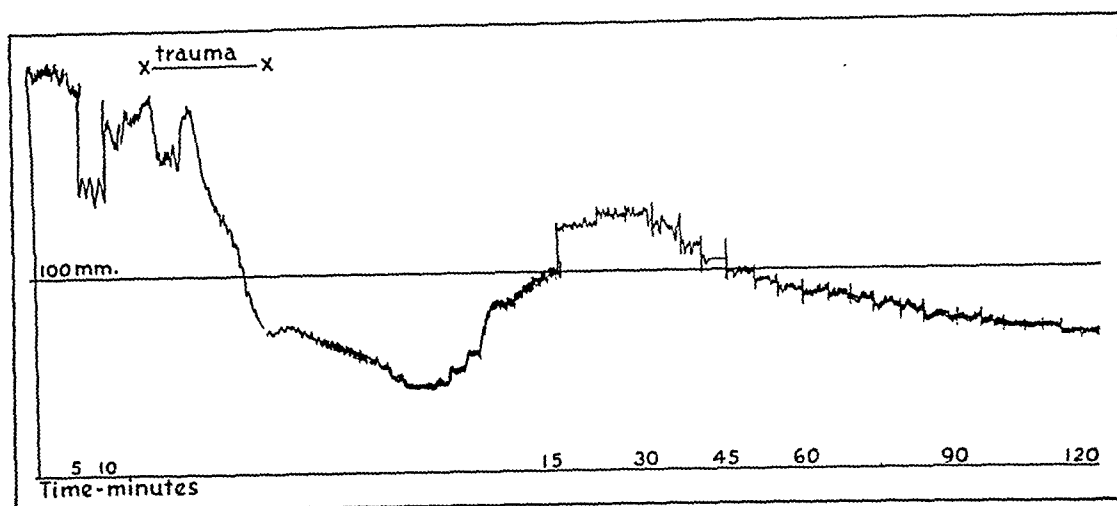


Fig. 3.—Blood pressure curve of a traumatized cat (weight, 2.7 Kg.) anesthetized with sodium barbital. At  $x-x$ , the left thigh was struck one hundred and fifty times. The loss of blood in the traumatized extremity measured 29.5 cc., or 15 per cent of the estimated blood volume.

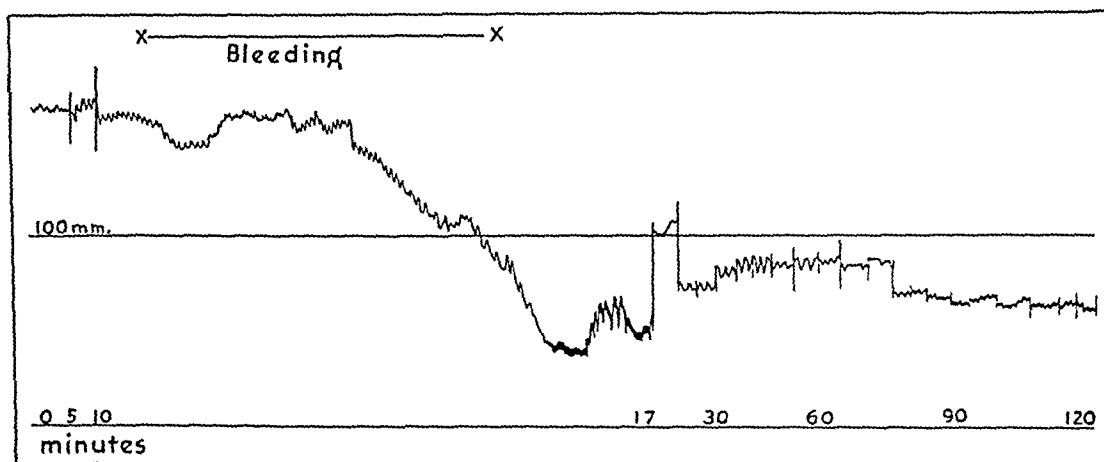


Fig. 4.—Blood pressure curve of a bled cat (weight, 3 Kg.) anesthetized with sodium barbital. At  $x-x$ , 34 cc. of blood, or 15 per cent of estimated blood volume, was taken from the left femoral artery. There was no trauma.

was the same. The pulse and respirations are similar whether the loss of blood was caused by bleeding or by trauma.

However, as the experiments progressed, it was evident that although individual cases of trauma and bleeding with the same loss of blood could be selected which were almost identical, nevertheless, in the whole



series of experiments, the animals traumatized seemed more severely injured than those bled. If we divide the animals into two groups according to the loss of blood, (1) those with a loss of from 20 to 30 per cent of the estimated blood volume and (2) those with a loss of from 10 to 20 per cent of the estimated blood volume, we find that in group 1 (table 6), of eight animals traumatized, four died in intervals of from eight minutes to one hour and thirty minutes, three had a blood pressure of below 80 mm. after an average period of three hours and one had

TABLE 5.—*Blood Estimation by Hemoglobin Method in Control Experiments*

Number	Original Blood, Cc.	Estimated Blood, Cc.
1.....	18	18.3
2.....	15	15.0
3.....	15	15.4
4.....	20	18.8
5.....	25	17.2
6.....	25	26.0
7.....	53	52.0
8.....	66	63.0
9.....	62	61.5
10.....	60	56.0

TABLE 6.—*Results in Traumatized Animals in Group 1\**

No.	Weight, Kg.	Loss of Blood, Cc.	Loss of Blood, per Cent of Volume (Estimated)	Initial Blood Pressure, Mm.	Final Blood Pressure, Mm.	Time	Hemoglobin (1),† per Cent	Hemoglobin (2),† per Cent	Per Cent of Change
28†	2.915	47.0	22	160	Died	1 hr. 30 min.	59	43	—27
29	3.300	53.7	22	160	55	3 hrs.	65	52	—20
30	3.085	46.6	21	175	80	4 hrs.	82	71	—15
31	2.350	35.6	21	135	Died	15 min.			
32†	3.015	46.5	21	150	Died	14 min.			
33	2.750	60.5	30	140	Died	8 min.			
34	2.690	54.8	28	140	55	4 hrs. 5 min.	62	51	—18
35	2.910	55.4	26	115	60	3 hrs. 10 min.	63	50	—21

\* In this group the loss of blood is from 1.4 to 2.1 per cent of the body weight, and from 20 to 30 per cent of the blood volume (estimated). The blood volume is estimated as one-fourteenth of the body weight, which is the figure given by Welcker for cats.

† The vessels were ligated immediately after trauma.

‡ Hemoglobin (1) was taken before trauma or hemorrhage, and hemoglobin (2) at the end of the experiment.

a blood pressure of over 80 mm. at the end of four hours. In nine animals bled the same amount (table 7), two died in an average period of two hours and fifty-five minutes, four had a blood pressure below 80 after a period of four hours and two had a blood pressure above 80 at the end of three hours and twenty minutes.

In group 2 in which the loss of blood was smaller, of eight traumatized animals (table 8), two died in two hours and twenty minutes, four had a blood pressure below 80 mm. at the end of three hours and two had a blood pressure of 80 or above in three hours and one half. Of ten animals bled an equal amount (table 9), none died, two had a blood pressure below 80 mm. at the end of three hours and thirty

minutes and eight had a blood pressure above 80 at the end of about three hours.

The similarity of the blood pressure curve in those traumatized and bled seems to establish hemorrhage as the chief factor in this form of traumatic shock. The more serious consequences following trauma (tables 10 and 11) can be explained by the added loss of fluid locally due to inflammatory edema which Blalock has shown to occur. Before dis-

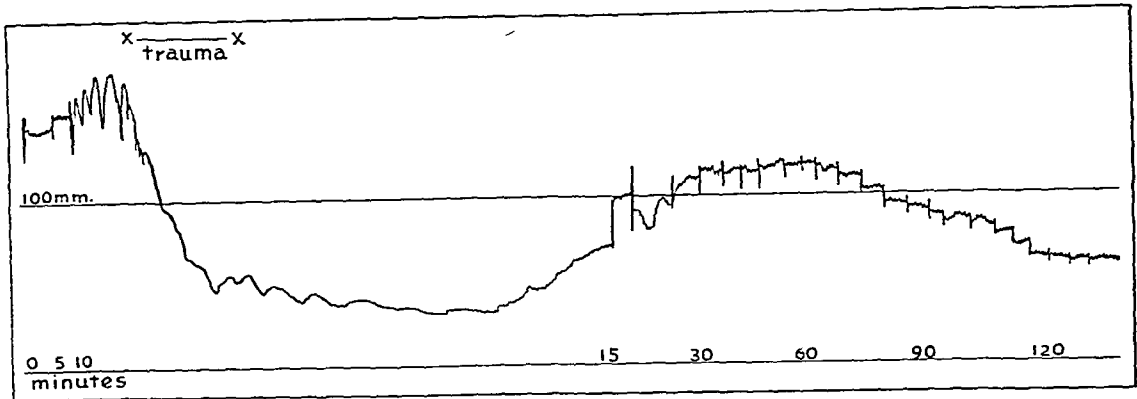


Fig. 5.—Blood pressure curve of a traumatized cat (weight, 2.7 Kg.) anesthetized with sodium barbital. At  $x-x$ , the left thigh was struck one hundred and fifty times. The loss of blood in the traumatized area measured 54.8 cc., or 29 per cent of the estimated blood volume.

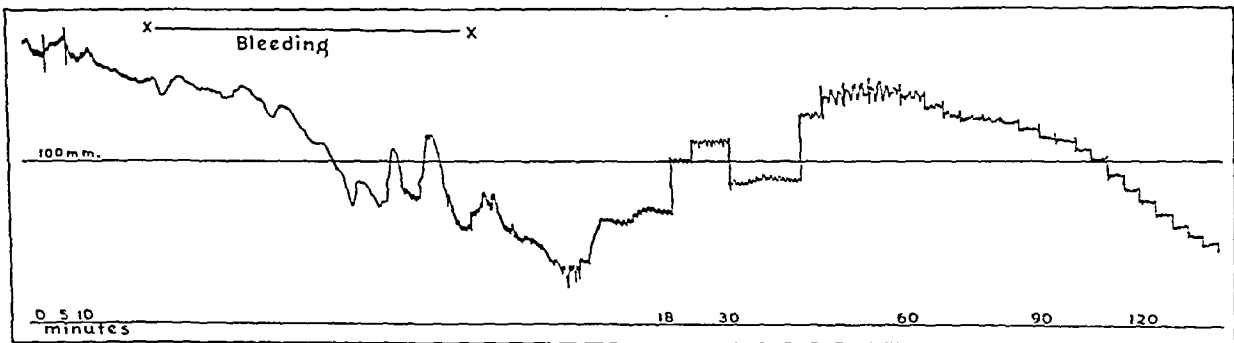


Fig. 6.—Blood pressure curve of a bled cat (weight, 3 Kg.) anesthetized with sodium barbital. At  $x-x$ , 66 cc. of blood, or 30 per cent of the estimated blood volume was taken from the left femoral artery. There was no trauma.

cussing this point, another factor must be mentioned. As has been stated, in the bled animals the arteries were tied immediately following trauma, while in the traumatized animals the blood vessels remained open. This may have influenced the final results in that, with the vessels open, even though the hemorrhage had stopped spontaneously, as the blood pressure rose, the bleeding might be resumed. However, in eight of the traumatized animals the iliac vessels were tied immediately fol-

lowing trauma. The blood pressure curves and end-results were similar to those experiments in which the vessels were not tied. It seems fair to conclude that it is the sudden acute hemorrhage that is responsible for the typical curve.

TABLE 7.—Results in Bled Animals in Group 1

No.	Weight, Kg.	Loss of Blood, Cc. (Estimated)	Loss per Cent of Blood Volume	Initial Blood Pressure, Mm.	Final Blood Pressure, Mm.	Time	Hemoglobin (1), per Cent	Hemoglobin (2), per Cent	Per Cent of Change
19	2.430	41	23	160	100	2 hrs. 45 min.	57	51	—11
20	2.460	40	22	125	Died	3 hrs. 25 min.			
21	2.725	47	23	140	75	4 hrs. 10 min.	61	43	—30
22	2.850	43	21	145	65	3 hrs. 45 min.	64	57	—11
23	2.79	42	21	170	50	3 hrs. 50 min.	56	44	—20
24	3.15	49	21	155	Died	2 hrs. 40 min.	56	44	—20
25	2.45	37	21	110	70	4 hrs. 45 min.	56	51	—9
26	3.015	66	30	160	Died	2 hrs. 25 min.	77	59	—24
27	2.495	50	29	155	90	3 hrs. 30 min.	80	62	—23

TABLE 8.—Results in Traumatized Animals in Group 2\*

No.	Weight, Kg.	Loss of Blood, Cc. (Estimated)	Loss per Cent of Blood Volume	Initial Blood Pressure, Mm.	Final Blood Pressure, Mm.	Time	Hemoglobin (1), per Cent	Hemoglobin (2), per Cent	Per Cent of Change
11†	2.700	29.0	15	160	60	3 hrs. 40 min.	74	60	—19
12	2.850	35.6	17	165	Died	2 hrs. 30 min.	63	40	—37
13†	2.58	34.0	18	160	50	2 hrs. 30 min.	71	56	—21
14†	2.94	41.7	19	180	Died	2 hrs. 10 min.			
15†	2.77	38.0	19	120	65	3 hrs. 5 min.	66	61	—8
16†	2.500	23.0	12	145	80	3 hrs. 30 min.	70	64	—8
17†	2.615	21.0	11	150	50	3 hrs. 10 min.	84	66	—22
18	2.562	23.4	12	150	115	3 hrs. 30 min.	82	75	—9

\* In this group the loss of blood was from 0.7 to 1.4 per cent of body weight, and from 10 to 20 per cent of the blood volume (estimated).

† The vessels were ligated immediately after trauma.

TABLE 9.—Results in Bled Animals in Group 2

No.	Weight, Kg.	Loss of Blood, Cc. (Estimated)	Loss per Cent of Blood Volume	Initial Blood Pressure, Mm.	Final Blood Pressure, Mm.	Time	Hemoglobin (1), per Cent	Hemoglobin (2), per Cent	Per Cent of Change
1	2.755	32	19	145	110	4 hrs. 5 min.	63	60	—5
2	3.400	44	18	145	90	3 hrs. 40 min.	65	49	—25
3	2.800	32	16	160	100	4 hrs.	75	67	—11
4	3.050	34	15	160	75	3 hrs. 50 min.	72	62	—14
5	2.975	35	16	140	120	3 hrs.	62	53	—15
6	2.530	27	15	100	110	3 hrs.	51	47	—8
7	2.85	31	15	150	110	2 hrs. 50 min.	72	65	—10
8	2.35	30	17	150	70	3 hrs. 5 min.	71	62	—13
9	2.72	40	20	130	105	4 hrs.	60	57	—5
10	2.757	21	10.6	130	105	3 hrs. 15 min.	56	54	—4

#### BLOOD AND TOTAL FLUID LOSS

In order to get some evidence as to the local fluid loss in addition to the hemorrhage, five cats were traumatized. the limbs weighed after

amputation at the sacro-iliac joint, and the loss of blood was estimated as in the previous experiments.

*Results.*—The difference in weight between the traumatized and untraumatized extremities ranged between 50 and 87 Gm., with an average of 68 Gm. This represented hemorrhage plus loss of fluid, which thus averaged about 40 per cent of the estimated blood volume (table 12). The loss of blood as calculated ranged from 36 to 52.7

TABLE 10.—*Summary in Group 2*

	Number of Animals	Died	Final Blood Pres- sure Above 80 Mm.	Final Blood Pres- sure Below 80 Mm.	Average Hemoglobin Reduction, per Cent
Hemorrhage.....	10	0	8	2	10.8
Trauma.....	8	2	2	4	14.5

TABLE 11.—*Summary in Group 1*

	Number of Animals	Died	Final Blood Pres- sure Above 80 Mm.	Final Blood Pres- sure Below 80 Mm.	Average Hemoglobin Reduction, per Cent
Hemorrhage.....	9	3	2	4	17.3
Trauma.....	8	4	0	4	18.5

TABLE 12.—*Blood and Total Fluid Loss in Traumatized Animals*

Number	Weight, Kg.	Loss of Blood (Estimated), Cc.	Loss of Blood, per Cent of Blood Volume (Estimated)	Difference in Weight of Traumatized and Untraumatized Limbs, Gm.	Total Loss of Fluid, per Cent of Blood Volume (Estimated)	Loss of Fluid Exclusive of Blood, per Cent of Blood Volume (Estimated)
1	2.940	40.5	19.0	50	23.6	4.6
2	2.135	36.1	23.0	54	35.0	12.0
3	2.310	38.2	23.1	73	44.0	20.9
4	2.385	48.1	28.0	87	51.0	23.0
5	2.480	52.7	27.9	78	45.0	18.0

cc., averaging 43 cc., or 23 per cent of the estimated blood volume. The difference between total fluid and loss of blood averaged 17 per cent of the blood volume. Therefore, local inflammatory edema caused an average loss of fluid of 17 per cent of the blood volume, a loss only 6 per cent less than the loss of blood. Even though the weight method of estimating loss of fluid is crude and inaccurate, yet the difference between loss of blood and gain in weight in the traumatized limb is so marked that it must represent a definite loss of fluid. This loss could account for the more severe effect in loss of blood from trauma than in bleeding from a vessel without trauma.

## LIGATION OF VESSELS

To show further the influence of hemorrhage on the blood pressure curve following trauma, experiments were done in which the left iliac artery and vein were ligated just before traumatizing the left thigh. Thirteen cats were used in this group.

*Results.*—There was no sharp drop in blood pressure during trauma in marked contrast to the control trauma experiments in which the vessels were not ligated (compare figure 7 and figure 1). However, in most of the experiments, after a latent period there was a slow moderate drop in blood pressure with almost complete recovery (table 13). This type of curve was occasionally observed in the control barbital experiments. Even though the chief vessels to the traumatized area were ligated, there was yet a moderate amount of hemorrhage and loss

TABLE 13.—*Results of Vessel Ligation in Traumatized Animals*

Number	Weight, Kg.	Initial Blood Pressure, Mm.	Final Blood Pressure, Mm.	Time	Loss of Blood, Cc.	Loss of Blood, per Cent of Blood Volume (Estimated)
1	3.21	143	145	3 hrs. 35 min.	15.0	6.1
2	3.00	180	150	3 hrs. 40 min.	7.9	3.6
3	2.7	132	94	3 hrs. 30 min.	11.5	6.0
4	2.88	160	130	3 hrs. 25 min.	9.4	4.5
5	3.5	140	155	2 hrs. 55 min.		
6	3.0	180	155	1 hr. 40 min.		
7	2.4	130	125	1 hr. 25 min.		
8	3.4	168	118	2 hrs. 25 min.		
9	2.3	160	120	2 hrs. 50 min.		
10	2.4	150	130	1 hr. 45 min.		
11	2.1	160	123	1 hr. 50 min.		
12	2.6	162	140	1 hr. 55 min.		
13	3.1	160	130	2 hrs. 5 min.		

of fluid. This loss of blood was measured in a few of the experiments and amounted to from 3 to 6 per cent of the estimated blood volume. Thus the slight effect of trauma on the blood pressure with the vessels ligated seems consistent with a small amount of hemorrhage.

## BLOOD CONCENTRATION

As the tables show, in both the bled and the traumatized animals, the hemoglobin concentration of the arterial blood was reduced. There was no evidence of blood concentration. The average reduction was 14.5 per cent in traumatized animals with a loss of blood of from 10 to 20 per cent of the blood volume, and 10.8 per cent in the animals bled this amount. When traumatized animals lost from 20 to 30 per cent in the blood volume, the hemoglobin reduction was 18.5 per cent, while in the animals bled this amount it was 17.3 per cent. This seems to furnish further evidence of the importance of hemorrhage as the chief factor in traumatic shock. It shows that in experiments done

under these conditions trauma is not followed by blood concentration. To check this point further in many of the controls both the hemoglobin and the total solids of the arterial blood were estimated (tables 1 and 2). The average reduction in hemoglobin for twenty-eight experiments was 15 per cent, while the average reduction in total solids for twelve experiments was 11.4 per cent. There were no experiments in which the blood showed concentration.

It is possible that the blood concentration found by other observers could have been due in some instances to the long duration of the experiments with resultant dehydration, and in others to the use of ether anesthesia. In our experience, ether anesthesia in dogs always gave rise to a concentration of blood of 10 to 15 per cent as estimated by hemoglobin determinations and occasionally it was as high as 40 per

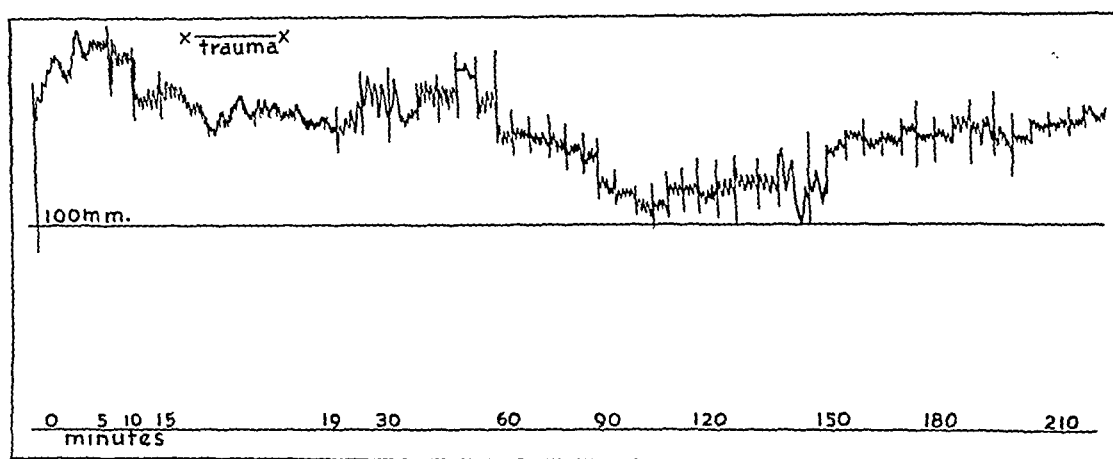


Fig. 7.—Blood pressure curve of a traumatized cat (weight, 3 Kg.) anesthetized with sodium barbital. The left iliac artery and vein were ligated before trauma. At  $x-x$ , the left thigh was struck one hundred and fifty times. The loss of blood was 3.6 per cent of the blood volume.

cent. In a series of experiments on dogs done under ether anesthesia, out of a hundred dogs, ten small animals either died or had a marked fall in blood pressure quickly, that is, within one-half hour after the anesthetic was started. All of these animals showed a blood concentration of over 25 per cent. This may explain the so-called shock seen so frequently in laboratory animals soon after an inhalation anesthetic is started.

#### SUMMARY

Cats weighing from 2 to 4 Kg. could be constantly shocked by traumatizing one posterior extremity with one hundred and fifty rapid blows of a wooden mallet. In a control series of forty animals, this brief unrepeatable trauma was followed by a typical blood pressure curve con-

sisting of a rapid fall in pressure during trauma, a rapid partial recovery, a level latent period, and then a slow fall into secondary shock. With this large series as a control, experiments were conducted to exclude all the nervous connections of the extremity to be traumatized. In order to accomplish this, recovery experiments were done in stages, cutting the cord, the peripheral nerves and the sympathetic chain. These completely denervated limbs responded to trauma like the controls.

The loss of blood in the traumatized limb was measured, and then other animals of comparable weight were rapidly bled these amounts. Rapid hemorrhage produced blood pressure curves similar in contour to those produced by trauma; however, with an equal loss of blood the end-results were more severe following trauma. Further experiments showed that following trauma in addition to the loss of blood there was a considerable local loss of fluid due to edema. Therefore, the added loss of fluid could account for the more severe symptoms following trauma. This confirms the findings of Blalock.

Measurements of the hemoglobin concentration in the arterial blood checked frequently by the estimation of total solids never showed any concentration following the drop in blood pressure but always a rather marked dilution. This dilution was similar to that following acute hemorrhage.

The shock following trauma can be explained on the basis of hemorrhage and local fluid loss.

## PERITONITIS

### II. SYNERGISM OF BACTERIA COMMONLY FOUND IN PERITONEAL EXUDATES

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In a previous paper, Meleney, Harvey and Jern presented the bacteriologic findings in a series of 106 cases of peritonitis.<sup>1</sup> They tried to correlate these findings with the clinical course. One of the most significant points brought out in that study seemed to be the fact that when two or more different species of intestinal organisms were present, the clinical course of the illness was much more serious than when a single species was present. This suggested the advisability of studying the synergistic or antagonistic effect of the organisms commonly found in peritonitis secondary to lesions of the intestine.

It has long been known that the intestinal tract habitually contains a number of different bacterial species that are constantly present from the time of early infancy until death. From time to time other organisms may gain a temporary foothold, but they generally come and go and leave the field to those that find the environment continually favorable to their growth. The different species survive in the presence of one another, and it seems reasonable to suppose that they have either an indifferent or a favorable effect on one another's presence. These intestinal bacterial species may be said to be living in a state of symbiosis. This term, taken literally, simply means the coexistence of two or more different species of organisms, but generally the term has a significance of mutual benefit. Some symbionts will not grow if separated from one another. Such a relationship is called an obligatory symbiosis. Others will grow better when together, but will grow to a limited degree if

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1. Meleney, F. L.; Harvey, H. D., and Jern, H. Z.: Peritonitis: I. The Correlation of the Bacteriology of the Peritoneal Exudates and the Clinical Course of the Disease in One Hundred and Six Cases of Peritonitis, *Arch. Surg.* **22**:1 (Jan.) 1931.



separated. Such a relationship is called a facultative symbiosis. On the negative side there are antagonisms in which certain species living in the same place inhibit one another. Then one or the other, or both, may be destroyed. Symbiosis may relate to more than two species living together. In the intestinal tract of man and of animals such is the case, and the relationship of the several species to the common host is not clearly understood. Some think that they are beneficial to the host, others think that they are detrimental, while others believe that the host is indifferent to their presence. When intestinal organisms invade the tissues of the host and give symptoms of disease, it is evident that, while they may be in symbiosis with one another, they are antagonistic to the host, and the host to them.

The term synergism is used when the symbionts are able to perform some function together that they cannot perform by themselves, or in which a function of one is greatly increased by the presence of the other.

#### HISTORICAL DATA

Symbiosis has been studied extensively by zoologists and botanists, but it has not been given the attention it should receive from the medical sciences. There is fossil evidence that symbiosis is a very ancient phenomenon of nature, and many believe that it is the most potent factor in the origin of species.<sup>2</sup>

One of the best examples of symbiotic existence is the lichen, which is formed by the intimate association of a fungus and an alga, and they are apparently in obligatory symbiosis. Fungi also grow around and in the roots of certain plants and trees, and this association is favorable for the growth of both of these species. Certain nitrifying bacteria that occur in the soil enter the root hairs of leguminous plants and supply the roots with nitrates, accepting in return carbohydrates for their own nourishment.<sup>3</sup>

Bacterial mixtures play an extremely important function in the disintegration of animal bodies, and this forms an important link in the cycle of life.

Symbiosis of bacteria has been observed in the laboratory for a long time, although since the time of Koch efforts have been made to obtain pure cultures and to study the biologic and cultural characteristics of the pure cultures, rather than to study the interaction or cooperative action of mixed cultures. Most of the observations that have been made with respect to bacterial synergism have been made by chance and have had no clinical importance, although they have frequently led to technical procedures of considerable commercial importance.<sup>4</sup> Most frequently, observations of the synergism of bacteria have been made with respect to the fermentation of carbohydrates and the digestion of proteins. A number of authors have shown that two or three different species of bacteria working together are able to perform a function that none of the single species can perform alone. In such circumstances it has been thought that one organism initiates the process

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2. Rheinheimer, H.: Symbiosis and Evolution, *J. Ment. Sc.* **69**:339, 1923.

3. Hastings, S.: Team-Work in Nature, *Lancet* **2**:774 (Oct. 6) 1923.

4. Sherman, J. M., and Shaw, R. H.: Associative Bacterial Action in the Propionic Acid Fermentation, *J. Gen. Physiol.* **3**:657, 1920. Speakman, H. B., and Phillips, J. F.: A Study of a Bacterial Association: I. The Biochemistry of the Production of Lactic Acid, *J. Bact.* **9**:183, 1924.

and the other finishes it, but in some instances, apparently, the organisms have to grow intimately with one another, and the synergistic effect is due to some interaction between the species.<sup>5</sup> Only a very limited number of observations have been reported with regard to the synergistic action of bacteria in disease processes. Castellani<sup>6</sup> listed three disease entities that he believed were due to synergistic action. Trichomycosis alba, trichomycosis rubra and stomatitis cryptococcus bacillaris are all diseases in which two organisms are constantly present, and both of them are necessary for the development of the disease. Vincent's angina is also considered to be due to two different species of organisms, a fusobacterium and a spirillum. Knorr<sup>7</sup> has presented evidence favoring the theory that the streptococcus of the mouth is a necessary accompaniment of these other organisms in the production of the disease. Liermann<sup>8</sup> made some interesting studies of bacterial mixtures in certain putrefactive processes and concluded that they were due to the synergistic action of several species, rather than to a single species. Bienstock<sup>9</sup> in his study of putrefactive organisms, observed that the association of anaerobes with aerobes was necessary for complete putrefaction. Kammerer<sup>10</sup> found that certain bacterial mixtures were essential for the production of hematoporphyrin from hemoglobin, and when he found hematoporphyrin in the fluid of lung abscesses he concluded that this action and possibly the lesion itself were due to a synergistic bacterial action. A very striking example of bacterial synergism was recently observed by one of us (Dr. Meleney) when two organisms that were recovered from a case of chronic empyema were studied. In this instance, the combined action of the organisms produced hemolysis on blood agar plates, when the colonies approximated one another.<sup>11</sup>

In 1926, Dr. Brewer took care of a patient in whom progressive gangrene of the abdominal wall developed following drainage of an appendical abscess. After conservative methods of treatment, the lesion was completely excised. In the periphery of the lesion, cultures yielded a pure micro-aerophilic streptococcus evidently of intestinal origin, while in the gangrenous zone this organism was combined with *Staphylococcus aureus*. When these organisms were injected into animals in pure culture, no lesion was obtained, but when they were combined they resulted in a violent infection with gangrene, indicating that they had some adjuvant

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5. Holman, W. L., and Meekison, D. W.: Gas Production by Bacterial Synergism, *J. Infect. Dis.* **39**:145, 1926. Castellani, A.: Fermentation Phenomenon When Different Species of Microorganisms Are in Close Association, *Proc. Soc. Exper. Biol. & Med.* **23**:481, 1926. Sears, H. J., and Putman, J. J.: Gas Production by Bacteria in Symbiosis, *J. Infect. Dis.* **32**:270, 1923.

6. Castellani, A.: Importance of Symbiosis or Close Association of Different Species of Organisms in the Production of Biochemical Phenomena and in the Causation of Certain Diseases and Certain Symptoms of Disease, *J. A. M. A.* **87**:15 (July 3) 1926; *J. Trop. Med.* **29**:217, 1926.

7. Knorr, M.: Ueber die fusospirillare Symbiose, die Gattung *Fusobacterium* und *Spirillum sputigenum*, *Centralbl. f. Bakt.* **87**:336, 1922.

8. Liermann, W.: Bakteriologische Untersuchungen über putride Intoxication, *Centralbl. f. Bakt.* **8**:364, 1890.

9. Bienstock: Untersuchungen über die Aetiologie der Eiweissfaulnis, *Arch. f. Hyg.* **36**:335, 1899.

10. Kammerer, H.: Beiträge zur Bedeutung des bakteriellen Synergismus für die Biologie, *Klin. Wchnschr.* **3**:725, 1924.

11. Meleney, F. L.: Aerobic and Anaerobic Examples of Hemolytic Bacterial Synergism, *Proc. Soc. Exper. Biol. & Med.* **24**:205, 1928.

action on one another and that the lesion was due to a synergism of these two species.<sup>12</sup> Recently a similar case yielded identical organisms, and experimental inoculation produced identical results, so that there seems to be very strong evidence in favor of the theory that this lesion is a disease due to the symbiosis and synergism of two bacterial species.<sup>13</sup>

In a recent study of organisms present in raw catgut (representing, of course, intestinal organisms of sheep, which were able to survive the drying process and the passage of time), Meleney and Chatfield found two specimens that yielded a combination of organisms which, when injected into laboratory animals, produced death, while these same organisms in pure culture failed to do so. In two other specimens the combination of organisms produced a skin necrosis that the pure cultures could not produce. Later on, while studying specimens of improperly sterilized catgut, they found two specimens that yielded a mixture of organisms that had a very prompt lethal effect on laboratory animals when injected together, but which in pure culture were entirely nonpathogenic.<sup>14</sup>

It has been known for a long time that there are two main bacteriologic groups of cases of peritonitis: (1) those that seem to appear spontaneously and (2) those that occur by a spread of organisms of some of the contained viscera. In the first or primary group, the causative organisms are generally hemolytic streptococcus or pneumococcus. In the other or secondary group, the peritoneal exudate frequently yields a number of bacterial species. Most of the workers in this field have tried to find out which of the several species was the significant one. Malvoz<sup>15</sup> and also Laruelle<sup>16</sup> attributed the primary rôle to *B. coli*. Tavel and Lanz,<sup>17</sup> who made a very exhaustive bacterial study, but without adequate anaerobic technic, stressed the fact that many of the cases were polymicrobial. They found a streptococcus frequently, but *C. welchii* very rarely. Their results seemed to indicate that the polymicrobial infections offered a better prognosis than the monomicrobial, but their study included the primary as well as the secondary peritoneal infections. A little later Veillon and Zuber<sup>18</sup> made studies of peritoneal exudates and discounted

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12. Brewer, G. E., and Meleney, F. L.: Progressive Gangrenous Infection of the Skin and Subcutaneous Tissues, Following Operation for Acute Perforative Appendicitis: A Study in Symbiosis, *Ann. Surg.* **84**:438 (Sept.) 1926.

13. Meleney, F. L.: Bacterial Synergism in Disease Processes: A Confirmation of the Synergistic Bacterial Etiology of a Certain Type of Progressive Gangrene of the Abdominal Wall, *Ann. Surg.* **94**:961 (Dec.) 1931.

14. Meleney, F. L., and Chatfield, M.: The Sterility of Catgut in Relation to Hospital Infections: With an Effective Test for the Sterility of Catgut, *Surg., Gynec. & Obst.* **52**:430 (Feb.) 1931.

15. Malvoz, E.: Le bacterium coli commune comme agent habituel des péritonites d'origine intestinale, *Arch. de méd. expér. et d'anat. path.* **3**:593, 1891.

16. Laruelle, L.: Etude bacteriologique sur les péritonitis par perforation, *Cellule* **5**:61, 1889.

17. Tavel, E., and Lanz, O.: Ueber die Aetiologie des Peritonitis, *Mitt. a. d. Klin. u. med. Inst. d. Schweiz.* **1**:1, 1893.

18. Veillon and Zuber: Recherches sur quelques microbes strictement anaérobies et leur rôle dans la pathologie humaine, *Arch. d. méd. expér. et d'anat. path.* **10**: 517, 1894.

the importance of the aerobes, laying particular stress on the anaerobes. These writers probably overemphasized the rôle of the anaerobes, but at least they called attention to them, and the recent workers have given them careful consideration. Heyde,<sup>19</sup> although he found *B. coli* to be the most frequent organisms in the peritoneal exudates that he studied, believed that it really played a subordinate rôle in the etiology of appendicitis and peritonitis. He laid more stress upon the gram-negative nonspore-forming anaerobic organism *B. thetoides*, although he was rarely able to demonstrate any pathogenicity of this organism in pure culture. Recently Weinberg and his associates<sup>20</sup> have reported studies of the purulent exudates in acute appendicitis. They received the appendixes in their laboratory, opened them from end to end and cultured the pus from the surface of the lesion. With this technic they could not avoid the intestinal organisms casually present, and it is difficult to evaluate their results on this account, but Weinberg takes a middle ground with respect to the significance of the aerobes and the anaerobes and brings out the possibility of a synergistic or symbiotic action of bacterial mixtures in the etiology of not only appendicitis but peritonitis. Weinberg found that in these exudates *B. coli* was by far the most common organism, occurring in 85 per cent. Intestinal streptococci were found in 30 per cent and Welch bacilli in 33 per cent. Anaerobic gram-negative bacilli were present in 39 per cent, and anaerobic cocci in 19 per cent. Although the aerobic species outnumbered the anaerobic in the whole series, the anaerobes predominated in the gangrenous cases, and Weinberg concluded that the gangrene was due to their presence. He found that the *B. coli* strains and the *C. welchii* strains were generally pathogenic for laboratory animals, but the other predominant organisms, previously mentioned, were for the most part innocuous when injected in pure culture. In association with the others, however, they seemed to become pathogenic themselves or to enhance the power of the associated organisms. Weinberg was handicapped by having no measure of the effect of the intestinal streptococcus when injected alone, as he found no pathogenic strains, but when small numbers were added to sublethal doses of *B. coli* or *C. welchii*, death ensued. In our study of the peritoneal exudates,<sup>1</sup> our method differed from that of Weinberg, for his exudates, within the appendix, represented abnormal intestinal contents, while our cultures represented organisms that were able to survive the defensive forces of the peritoneum. We believe that our results,

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19. Heyde, M.: Bakteriologische und experimentelle Untersuchungen zur Aetiologie der Wurmfortsatzentzündung (mit besonderer Berücksichtigung der anaëroben Bakterien), Beitr. z. klin. Chir. **76**:1, 1911.

20. Weinberg, M.; Prevot, A. R.; Davesne, J., and Renard, C.: Recherches sur la bactériologie et la sérothérapie des appendicitis aiguës, Ann. Inst. Pasteur **42**:1167, 1928.

therefore, more nearly present the significant organisms in the peritoneal infection. The outstanding organisms in our series were *B. coli*, non-hemolytic streptococcus (a large group) and *C. welchii*. *B. thetoides* was only rarely found and was always nonpathogenic.

In cases of peritonitis such as one sees clinically there seems to be evidence that the infection is due to the organisms habitually present within the intestine rather than to the introduction of organisms not commonly found there. Mechanical accidents, such as a gunshot wound, a local ulceration or injury to the intestine from within or an interference of the blood supply of a part of the intestine, permit the organisms to invade the wall and pass through it into the peritoneal cavity. There is both clinical and experimental evidence to show that the peritoneum is able to overcome contamination with intestinal organisms provided that they are not introduced into the peritoneal cavity in too great numbers or at too great a speed, but if such limits are exceeded, peritonitis and death may ensue. In clinical cases, if there is no gross perforation of the wall, certain organisms may pass through the wall of the intestine or may be carried through by phagocytic cells in sufficient numbers for them to gain a foothold and multiply within the peritoneal cavity. Such organisms are of moderate pathogenicity. If there is a gross perforation of the intestine, numerous varieties of intestinal organisms, both pathogenic and nonpathogenic, enter the peritoneal cavity and not only may survive, but may multiply in this new environment. Usually only those of definite pathogenicity continue to multiply, and if the peritoneum finally gets the infection under control, one by one the different species that were originally present disappear from the peritoneal exudate. The survival of different species in the drainage tracts of peritoneal infections is being studied and will be reported later.

#### EXPERIMENTAL DATA

The present study has to do solely with the lethal effect of intraperitoneal injections into laboratory animals of the bacteria most frequently found in peritoneal exudates both in pure and in mixed cultures, namely, *B. coli*, nonhemolytic streptococcus and *C. welchii*.

*Pathogenicity.*—When these organisms are isolated and grown in pure culture and are injected into the peritoneal cavity of laboratory animals, it has been found that their pathogenicity varies considerably. When first isolated from the human body, minimal lethal doses of *B. coli* for guinea-pigs weighing 250 Gm. are in the neighborhood of 250,000,000, and for mice, 50,000,000. With *C. welchii* the intraperitoneal lethal dose is around 2,500,000,000 for guinea-pigs and 500,000,000 for mice. With streptococci very often doses of from 50,000,000,000 to 100,000,000,000 fail to kill guinea-pigs, while those

of from 10,000,000,000 to 20,000,000,000 often fail to kill mice. One of our strains, however, regularly killed when given in doses of between 5,000,000,000 and 10,000,000,000.

*Bacterial Count.*—The numerical estimate of bacteria was made with the Gates<sup>21</sup> turbidimeter, with a standard suspension of streptococci containing 2,000,000,000 to the milliliter as a control. The fact that *B. coli* is smaller and *C. welchii* larger than streptococci probably suggests that a relatively larger number of *B. coli* and a smaller number of *C. welchii* are necessary to attain the same degree of turbidity.

*Increasing Virulence.*—The virulence of our *B. coli* strains could very frequently be increased by repeated animal inoculations, and the minimal lethal dose was often lowered to 10,000,000 for guinea-pigs and 1,000,000 for mice. With *C. welchii*, repeated rapid animal inoculations very rarely increased the minimal lethal dose; in fact, it was usually better to pass it rapidly through artificial culture mediums than through animals. This is perhaps indicative of its essentially saprophytic nature. We could almost never increase the virulence of the intestinal streptococci. With all of these organisms, the minimal lethal dose varied from month to month, from week to week and even from day to day, and the variation in resistance of individual animals made quantitative experiments extremely difficult. This was true to a greater degree in guinea-pigs or rabbits than in mice because of the variation in size, weight and previous contact with infection. For the foregoing reasons any experiments depending on multiples, or fractions of, the minimal lethal dose are subject to variations in their results unless these changeable factors can be fairly adequately controlled.

*Stabilizing Conditions.*—The control of changeable factors is favored by using mice of approximately equal weight and by a determination of the minimal lethal dose of the organisms to be tested on the day preceding the experiment. It is important also to use only young cultures in a phase of active growth.<sup>22</sup> We have used in our experiments from four to eight hour cultures that are planted in the morning and injected in the afternoon, thus insuring the viability of a large proportion of the organisms injected. At first we had considerable difficulty with the virulence of *B. coli*. Finally we found that in almost every culture there are two types of colonies, one dark and the other pale, as seen by light transmitted through a blood agar plate. To reflected light, the dark colonies appear light, and the pale colonies appear dark. The light colonies by transmitted light are only slightly nonpathogenic, while the dark colonies maintain a fairly high and constant pathogenicity. It is important,

21. Gates, F. L.: A Method of Standardizing Bacterial Suspensions, *J. Exper. Med.* **31**:105 (Jan.) 1920.

22. Chesney, A. M.: The Latent Period in the Growth of Bacteria, *J. Exper. Med.* **24**:387, 1916.

therefore, to transplant dark colonies initially into the broth from which the inoculation into the final culture is made. With *C. welchii* there are variations in the colonies that do not seem to have the same significance from the point of view of pathogenicity.

*Source of Our Cultures.*—We obtained our cultures of *B. coli*, green streptococcus and *C. welchii* from the exudate in an infected abdominal wound in a patient in whom a resection of the intestine had been performed. The initial pathogenicity of all of these organisms for mice and guinea-pigs was unusually high. The minimal lethal dose (M.L.D.)

TABLE 1.—*Intraperitoneal Injections of B. Coli and C. Welchii, Alone and Together\**

Mice	B. Coli	C. Welchii	Both		Result
			B. Coli	C. Welchii	
1	10 M	.....	.....	.....	Died over night
2	.....	800 M	.....	.....	Died over night
3	.....	.....	5 M	400 M	Died over night
4	5 M	.....	.....	.....	Died over night
5	.....	400 M	.....	.....	Died over night
6	.....	.....	2.5 M	200 M	Died over night
7	2.5 M	.....	.....	.....	Died over night
8	.....	200 M	.....	.....	Survived
9	.....	.....	1.25 M	100 M	Died over night
10	1.25 M	.....	.....	.....	Survived
11	.....	100 M	.....	.....	Survived
12	.....	.....	625 T	50 M	Died over night
13	625 T	.....	.....	.....	Survived
14	.....	50 M	.....	.....	Survived
15	.....	.....	313 T	25 M	Survived
16	.....	.....	156 T	12.5 M	Died over night
17	.....	.....	78 T	6.3 M	Sick; survived

M.L.D. in this test: *B. coli*, 2,500,000; *C. welchii*, 400,000,000

Fatal dose of mixtures: 1/2 M.L.D. of *B. coli* + 1/4 M.L.D. of *C. welchii*  
 1/4 M.L.D. of *B. coli* + 1/8 M.L.D. of *C. welchii*  
 1/16 M.L.D. of *B. coli* + 1/32 M.L.D. of *C. welchii*

\* Previously estimated minimal lethal doses: *B. coli*, 5,000,000; *C. welchii*, 500,000,000. B indicates billion; M, million; T, thousand; M.L.D., minimal lethal dose.

for white mice of *B. coli* approximated from 1,000,000 to 5,000,000; of *C. welchii* from, 200,000,000 to 400,000,000, and of green streptococcus, from 1,000,000,000 to 10,000,000,000.

*Method.*—We made all of the four possible combinations with these three organisms, using two together and then all three together, and repeated the experiments several times with entirely consistent results. Tables 1 to 4 show the protocols of typical experiments. Our pure cultures were obtained by repeated plating and fishing, and the stock cultures were kept on cooked meat medium. Fresh inoculations were made from the stock cultures (or from dark colonies in the case of *B. coli*), two days before the day of the experiment, into cooked meat mediums with 0.2 per cent dextrose for overnight growth. In the morning these cultures were seeded into a fresh cooked meat medium with

TABLE 2.—*Intraperitoneal Injections of B. Coli and Green Streptococcus, Alone and Together \**

Mice	B. Coli	Green Streptococcus	Both		Result
			B. Coli	Green Streptococcus	
1	10 M	.....	.....	.....	Died over night
2	.....	10 B	.....	.....	Died over night
3	.....	.....	5 M	5 B	Died over night
4	5 M	.....	.....	.....	Died over night
5	.....	5 B	.....	.....	Sick; survived
6	.....	.....	2.5 M	2.5 B	Died over night
7	2.5 M	.....	.....	.....	Died over night
8	.....	2.5 B	.....	.....	Survived
9	.....	.....	1.25 M	1.25 B	Died over night
10	1.25 M	.....	.....	.....	Died over night
11	.....	1.25 B	.....	.....	Survived
12	.....	.....	625 T	625 M	Died over night
13	625 T	.....	.....	.....	Survived
14	.....	625 M	.....	.....	Survived
15	.....	.....	313 T	313 M	Died over night
16	.....	.....	156 T	156 M	Died over night
17	.....	.....	78 T	78 M	Died in 40 hours

M.L.D. in this test: B. coli, 1,250,000; green streptococcus, 10,000,000,000

Fatal dose of mixtures: 1/2 M.L.D. of B. coli + 1/16 M.L.D. of green streptococcus  
1/4 M.L.D. of B. coli + 1/32 M.L.D. of green streptococcus  
1/8 M.L.D. of B. coli + 1/64 M.L.D. of green streptococcus  
1/16 M.L.D. of B. coli + 1/128 M.L.D. of green streptococcus

\* Previously estimated minimal lethal doses: B. coli, 5,000,000; green streptococcus, from 5,000,000,000 to 10,000,000,000. B indicates billion; M, million; T, thousand; M.L.D., minimal lethal dose.

TABLE 3.—*Intraperitoneal Injections of C. Welchii and Green Streptococcus, Alone and Together \**

Mice	C. Welchii	Green Streptococcus	Both		Result
			C. Welchii	Green Streptococcus	
1	1 B	.....	.....	.....	Died over night
2	.....	15 B	.....	.....	Died over night
3	.....	.....	500 M	7.5 B	Died over night
4	500 M	.....	.....	.....	Died over night
5	.....	7.5 B	.....	.....	Died over night
6	.....	.....	250 M	3.75 B	Died over night
7	250 M	.....	.....	.....	Died over night
8	.....	3.75 B	.....	.....	Died, 22 hours
9	.....	.....	125 M	1.88 B	Died, 22 hours
10	125 M	.....	.....	.....	Survived
11	.....	1.88 B	.....	.....	Survived
12	.....	.....	62.5 M	0.94 B	Died, 36 hours
13	62.5 M	.....	.....	.....	Survived
14	.....	940 M	.....	.....	Survived
15	.....	.....	31.3 M	470 M	Died, 48 hours
16	.....	.....	15.6 M	235 M	Sick; survived
17	.....	.....	7.8 M	117 M	Died, 24 hours

M.L.D. in this test: C. welchii, 250,000,000; green streptococcus, 3,750,000,000

Fatal dose of mixtures: 1/4 M.L.D. of C. welchii + 1/4 M.L.D. of green streptococcus  
1/8 M.L.D. of C. welchii + 1/8 M.L.D. of green streptococcus  
1/32 M.L.D. of C. welchii + 1/32 M.L.D. of green streptococcus

\* Previously estimated minimal lethal doses: C. welchii, 500,000,000; green streptococcus, from 5,000,000,000 to 10,000,000,000. B indicates billion; M, million; M.L.D., minimal lethal dose.



0.2 per cent dextrose and grown for from four to eight hours. Their number was then determined with the Gates turbidimeter, and dilutions were made in buffered phosphate broth for a preliminary determination of the minimal lethal dose. After the minimal lethal dose of the two organisms to be tested had been determined in a preliminary series of animals, on the next day another series was given injections of these organisms in pure and in mixed culture as follows: Number 1 in the

TABLE 4.—*Intraperitoneal Injections of B. Coli, C. Welchii and Green Streptococcus, Alone and Together*

Mice	B. Coli	C. Welchii	Green Streptococcus	All Three			Result
				B. Coli	C. Welchii	Green Strep-tococcus	
1	10 M	.....	.....	.....	.....	.....	Died over night
2	.....	1 B	.....	.....	.....	.....	Died over night
3	.....	.....	10 B	.....	.....	.....	Died over night
4	.....	.....	.....	3.3 M	0.3 B	3.3 B	Died over night
5	5 M	.....	.....	.....	.....	.....	Died over night
6	.....	0.5 B	.....	.....	.....	.....	Died over night
7	.....	.....	5 B	.....	.....	.....	Died over night
8	.....	.....	.....	1.7 M	167 M	1.7 B	Died over night
9	2.5 M	.....	.....	.....	.....	.....	Died, 40 hours
10	.....	0.25 B	.....	.....	.....	.....	Died over night
11	.....	.....	2.5 B	.....	.....	.....	Died over night
12	.....	.....	.....	0.8 M	83 M	0.8 B	Died over night
13	1.25 M	.....	.....	.....	.....	.....	Survived
14	.....	0.125 B	.....	.....	.....	.....	Survived
15	.....	.....	1.25 B	.....	.....	.....	Survived
16	.....	.....	.....	0.4 M	42 M	0.4 B	Died over night
17	0.63 M	.....	.....	.....	.....	.....	Survived
18	.....	63 M	.....	.....	.....	.....	Survived
19	.....	.....	0.62 B	.....	.....	.....	Survived
20	.....	.....	.....	0.2 M	21 M	0.2 B	Sick; survived
21	.....	.....	.....	0.1 M	10 M	0.1 B	Died, 48 hours
22	.....	.....	.....	50 T	5 M	50 M	Survived

M.L.D. in this test: B. coli, 2,500,000; C. welchii, 250,000,000; green streptococcus, 2,500,000,000

Fatal dose of mixtures:

1/6 M.L.D. of B. coli + 1/6 M.L.D. of C. welchii + 1/6 M.L.D. of green streptococcus

1/24 M.L.D. of B. coli + 1/24 M.L.D. of C. welchii + 1/24 M.L.D. of green streptococcus

\* Previously estimated minimal lethal doses: B. coli, 5,000,000; C. welchii, 500,000,000; green streptococcus, 5,000,000,000. B indicates billion; M, million; T, thousand; M.L.D., minimal lethal dose.

series received something more than one minimal lethal dose of one organism. Number 2 received a corresponding dose of the other organism. Number 3 received one half of each of these. The fourth animal received one half of the original dose of the first organism. Number 5 received one half of the original dose of the second organism, and number 6, one half of each of these, and so on. When the doses of pure culture were well below the estimated minimal lethal doses. the last three or four animals received simply one half of the dose of the mixture used with the preceding animal in the series, until the dilution was carried down to small fractions of the minimal lethal dose. When

all three of the species were combined, the mixture contained one third of the dose of the pure cultures. Thus the variability of the minimal lethal dose was controlled, and the actual minimal lethal dose under the conditions of the experiment was determined.

*Results.*—In almost every experiment it was possible to demonstrate that the mixtures of the organisms produced a lethal effect in considerably smaller doses than the pure cultures. Tables 1 to 4 indicate clearly the results that we obtained with these organisms when injected into mice. It will be seen in table 1 that three small fatal doses of the mixture of *B. coli* and *C. welchii* contained:

$\frac{1}{2}$  M.L.D. of *B. coli* +  $\frac{1}{4}$  M.L.D. of *C. welchii*,  
 $\frac{1}{4}$  M.L.D. of *B. coli* +  $\frac{1}{8}$  M.L.D. of *C. welchii*,  
 and  $\frac{1}{16}$  M.L.D. of *B. coli* +  $\frac{1}{32}$  M.L.D. of *C. welchii*, respectively.

Table 2 shows that four small fatal doses of the mixture of *B. coli* and green streptococcus contained:

$\frac{1}{2}$  M.L.D. of *B. coli* +  $\frac{1}{16}$  M.L.D. of green streptococcus,  
 $\frac{1}{4}$  M.L.D. of *B. coli* +  $\frac{1}{32}$  M.L.D. of green streptococcus,  
 $\frac{1}{8}$  M.L.D. of *B. coli* +  $\frac{1}{64}$  M.L.D. of green streptococcus,  
 and  $\frac{1}{16}$  M.L.D. of *B. coli* +  $\frac{1}{128}$  M.L.D. of green streptococcus, respectively.

Table 3 shows that three fatal doses of the mixture of *C. welchii* and green streptococcus contained:

$\frac{1}{4}$  M.L.D. of *C. welchii* +  $\frac{1}{4}$  M.L.D. of green streptococcus  
 $\frac{1}{8}$  M.L.D. of *C. welchii* +  $\frac{1}{8}$  M.L.D. of green streptococcus  
 and  $\frac{1}{32}$  M.L.D. of *C. welchii* +  $\frac{1}{32}$  M.L.D. of green streptococcus, respectively.

Table 4 shows that two fatal doses of the mixture of *B. coli*, *C. welchii* and green streptococcus contained:

$\frac{1}{6}$  M.L.D. of *B. coli* +  $\frac{1}{6}$  M.L.D. of *C. welchii* +  $\frac{1}{6}$  M.L.D. of green streptococcus and  $\frac{1}{24}$  M.L.D. of *B. coli* +  $\frac{1}{24}$  M.L.D. of *C. welchii* +  $\frac{1}{24}$  M.L.D. of green streptococcus, respectively.

#### COMMENT AND SUMMARY

We have experimented with the organisms commonly found in peritoneal exudates, namely, *B. coli*, nonhemolytic streptococcus and *C. welchii*, with the purpose of determining, if possible, their synergistic action in producing fatal peritonitis following intraperitoneal injection. We have determined the minimal lethal dose of each organism in pure culture and have found that the minimal lethal dose of *B. coli* when first isolated from either man or animals and injected intraperitoneally into animals is consistently less than the minimal lethal dose of *C. welchii* and considerably less than the minimal lethal dose of the intestinal streptococci. Furthermore, the virulence of *B. coli* may be increased by repeated animal inoculation, but *C. welchii* and the

intestinal streptococci are rarely amenable to this enhancement. While it is not proper to conclude that this relative pathogenicity in animals applies to man also, the foregoing facts are consistent with the clinical observations in our first paper, which indicated that *C. welchii* is not particularly virulent in the peritoneal cavity and that it is essentially saprophytic rather than pathogenic.

In order to achieve consistent results in experiments involving quantitative measurements, we found it necessary to stabilize conditions as far as possible. When dealing with organisms of low virulence, the effects of any variables are greatly magnified. In order to minimize the effects of variable factors, we took the following precautions: We made a preliminary determination of the minimal lethal dose of each organism just before the experiment in which it was used. We inoculated young bacterial cultures from four to eight hours old in an active growth phase and with the Gates turbidimeter made as accurate as possible a determination of the numbers of organisms present in the inoculum. We used enough animals in each experiment to be sure that moderate variations in the minimal lethal dose from day to day would not nullify the experiment. We used white mice of uniform size from the same brood. With these precautions our results were consistent.

We made all of the four possible combinations with the three species of organisms commonly found in peritoneal exudates. *B. coli* was combined with green streptococcus and with *C. welchii*. Green streptococcus was then combined with *C. welchii*, and lastly all three were combined. The experiments consisted of injecting intraperitoneally into a series of white mice constant multiples and constant fractions of the preliminary minimal lethal dose for each pure culture and each combination, and the lethal effects were observed. Tables 1 to 4 show that when any two or all three of these organisms were combined, the mixture was lethal in quantities considerably less than the lethal doses of the pure cultures. Death of the animals occurred with these mixtures in doses ranging from one-tenth to one-fifteenth of the lethal dose of the pure cultures.

The nature of this lethal effect has not been determined. It may be due simply to the growth-stimulating effect of one organism on the other, or it may indicate the production of some toxic product by the synergistic action of the combined organisms that neither can produce alone. The first explanation is not borne out by test tube experiments. In view of the other synergistic effects about which we know, the latter theory is quite within the range of possibility, but it is difficult to prove.

The tables further indicate that each species had an adjuvant effect on the other two, and in this respect no one species stands out as being more effective than the others. This corresponds strikingly with the clinical observations reported in the first paper and bears out the opinion

there expressed that, contrary to general belief, *C. welchii* is not more active than the other two organisms in peritoneal infections, and the consequences of its presence are not more serious.

#### CONCLUSIONS

The bacteria commonly found in peritoneal exudates, namely, colon bacillus, green streptococcus and Welch bacillus, have a synergistic action in producing a lethal infection of the peritoneum. They kill in much smaller doses when two or three of the species are combined than when inoculated in pure culture. The Welch bacillus is not more active in this synergistic action than the other two.

Smears and cultures of the peritoneal exudate should be made at the time of operation in cases of peritonitis in order that there may be a basis for prognosis. If the cultures reveal more than one species of intestinal organism, the prognosis is likely to be worse than if any one organism is found in pure culture. (This does not apply to the primary forms of peritonitis usually due to hemolytic streptococcus or pneumococcus.)

Any study of experimental or clinical peritonitis from a bacteriologic point of view must take into consideration not only the adjuvant action of one species of intestinal bacteria on the others, but the possibility of a toxic substance formed by the synergism of these bacteria when growing together in mixed cultures which may not be produced by any one of the species in pure cultures.

# THE BREAKING STRENGTH OF HEALING FRACTURED FIBULAE OF RATS

## IV. OBSERVATIONS ON A HIGH CARBOHYDRATE DIET

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In previous papers we have considered the effect of a standard diet<sup>1</sup> and of a high fat diet<sup>2</sup> on the breaking strength of healing fractured fibulae in albino rats. In our present paper we shall report the results of a study of the influence exerted on the breaking strength of similar fractures by a high carbohydrate diet.

The absorption of calcium and phosphorus from the gastro-intestinal tract has been shown to be favored by acidic intestinal contents.<sup>3</sup> Consequently the foods that produce such contents are advantageous in the assimilation of these salts. Lactose, for one, establishes acid-producing flora in the intestine, while corn starch changes the reaction of the tract but slightly.<sup>4</sup> In agreement with the changes in the hydrogen ion concentration produced by these two carbohydrates, it has been demonstrated experimentally that lactose increases the absorption of calcium and phosphorus, while starch diets are followed by inconsequential changes in the normal quantity of salts taken into the circulation from

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The expense of this investigation was defrayed by Davis and Geck, Inc.

1. McKeown, R. M.; Lindsay, M. K.; Harvey, S. C., and Howes, E. L.: The Breaking Strength of Healing Fractured Fibulae of Rats: II. Observations on a Standard Diet, *Arch. Surg.* **24**:458 (March) 1932.

2. McKeown, R. M.; Lindsay, M. K.; Harvey, S. C., and Lumsden, R. W.: The Breaking Strength of Healing Fractured Fibulae of Rats: III. Observations on a High Fat Diet, *Arch. Surg.* **25**:467 (Sept.) 1932.

3. Orr, W. J.; Holt, L. E., Jr.; Wilkins, L., and Boone, F. H.: The Relation of Calcium and Phosphorus in the Diet to the Absorption of These Elements from the Intestine, *Am. J. Dis. Child.* **28**:574 (Nov.) 1924. Irving, L., and Ferguson, J.: *Proc. Soc. Exper. Biol. & Med.* **22**:527, 1925.

4. Mitchell, H. S.: *Am. J. Physiol.* **79**:537, 1927.

the intestine.<sup>5</sup> Lactose, however, is poorly tolerated and results in clearly defined deleterious symptoms when fed in excess amount for a period of time.<sup>6</sup> Starch, on the other hand, satisfies the carbohydrate requirements, is well tolerated and permits a normal calcium and phosphorus metabolism.<sup>5</sup>

The metabolic correlation between the metabolism of carbohydrates and phosphorus has been shown by a number of workers<sup>7</sup> to be close. It has been demonstrated that the ingestion of a large amount of carbohydrate is followed by a sharp fall in the serum inorganic phosphate.<sup>8</sup> The disappearance of the phosphates is believed by these workers to be due to their combination with certain carbohydrates, forming among other compounds, hexose phosphates and glycerophosphates. It is these particular forms of phosphates that appear to be especially concerned in the hydrolytic reaction with the bone esterase phosphatase, the end-product of the reaction being phosphate in a form suitable for the growth, development and repair of bone.<sup>9</sup> One might assume from the foregoing data that an increase in the carbohydrate-phosphate compounds in the blood stream following the administration of a high carbohydrate diet would result in an increase in the reparative process of fractures due to the greater quantity of carbohydrate-phosphates available for hydrolysis by phosphatase. Our results are not, however, in accord with such an assumption.

The relationship existing between the metabolism of calcium and carbohydrates is not apparently as well understood as is that of phosphorus. We do know, however, that calcium and phosphorus tend to maintain a relatively constant ratio,<sup>10</sup> and that as the one varies the other likewise varies in an effort to maintain a constant balance.<sup>11</sup> Theoretically, it is possible that with a reduction in the organic phosphates of the serum, following ingestion of quantities of carbohydrates, the calcium would in turn be reduced through an increase in the amount of it excreted by the normal channels in an attempt to restore the ratio. Should this take place, healing of fractures under such conditions would be less complete than otherwise, and the breaking strength of the callus would be correspondingly reduced. In addition to the foregoing possi-

5. Bergeim, O.: *J. Biol. Chem.* **70**:35, 1926.

6. Block, C. E.: *Brit. M. J.* **1**:293, 1921.

7. Bolliger, A., and Hartman, F. W.: *J. Biol. Chem.* **64**:91, 1925. Harrop, G. A., and Benedict, E. M.: *J. Biochem.* **59**:683, 1924.

8. Lambie, C. G., and Redhead, F. A.: *Biochem. J.* **21**:549, 1927.

9. Martland, M., and Robison, R.: *Biochem. J.* **23**:237, 1929. Kay, H. D.: *ibid.* **20**:798, 1926. Goodwin, H. W., and Robison, R.: *ibid.* **18**:1161, 1924.

10. Hoag, J. R., and Palmer, L. S.: *J. Biol. Chem.* **76**:367, 1928.

11. Bethke, R. M.; Steenbock, H., and Nelson, M.: *J. Biol. Chem.* **58**:71, 1923.

bility, it has also been shown that the hypoglycemic state of parathyroid tetany can be obviated by injections of calcium salts, as well as by solutions of dextrose.<sup>12</sup>

Some interdependence between carbohydrate and calcium metabolism evidently does exist, but we are in possession of little experimental knowledge concerning it.

#### PROCEDURE

The routine technic adopted for this series of studies has been given in detail before.<sup>13</sup> The Moise and Smith high carbohydrate diet<sup>14</sup> was used in this investigation. Corn starch furnishes the elevated carbohydrate percentage, and was the most suitable form for our purposes.

In addition to this diet, 100 mg. of dried yeast powder was fed every second day. The salt mixture was the same Osborne and Mendel<sup>15</sup> preparation described in former papers, but differed in being 0.8 per cent less in quantity than in the standard diet, and 2.8 per cent less than in the high fat food. The differences in the quantity of salt in each of the foregoing diets were due to the known

#### *High Carbohydrate Diet*

	Percentage	Calories per Kilogram of Food		Apportionment of Total Calories
Casein.....	14.0	514	Protein.....	13.8
Starch (corn).....	79.0	3,239	Carbohydrate...	77.8
Cod liver oil.....	3.8	353	Fat.....	8.4
Salts.....	3.2			
		4,166		

differences in the amounts of the various diets that the animals would consume. Smith and Carey<sup>16</sup> established this fact several years ago when they showed that rats ate for calories. They adjusted the salt content of their diets in such a fashion that, regardless of a reduction or an elevation in the ingestion of the particular diet under study, the amount of salt taken in remained comparatively constant. Owing to this correction, it is permissible to consider the salt intake on each of the three diets to be relatively the same.

At the expiration of one week on the diet, the animals were divided into two groups. The first group, known as the "high carbohydrate fracture," was divided into fourteen lots of seven animals to each lot. The right fibula of every animal in this group was fractured in the manner described before,<sup>13</sup> and beginning on the sixth postoperative day and continuing at intervals of three days thereafter for the fourteen time periods, the entire lot of seven on that particular time period was killed. After suitable preparation the breaking and healing strengths of the unfractured left and the fractured right fibulae, respectively, were determined in the manner described before.<sup>13</sup>

12. Cori, C. F., and Cori, G. T.: *J. Biol. Chem.* **79**:321, 1928. Reed, C. I.: *Am. J. Physiol.* **89**:230, 1929.

13. McKeown, Lindsay, Harvey and Howes (footnote 1). McKeown, Lindsay, Harvey and Lumsden (footnote 2).

14. Moise, T. S., and Smith, A. H.: *J. Exper. Med.* **40**:13, 1924.

15. Osborne, T. B., and Mendel, L. B.: *J. Biol. Chem.* **37**:557, 1919.

16. Smith, A. H., and Carey, E.: *J. Biol. Chem.* **53**:425, 1923.

The second group, called the "high carbohydrate control" to distinguish it from the fractured group, was free from fractures and had also been on the diet for one week. At the same time the fibulae were fractured in the fractured rats, this second group was divided into lots of four, and a lot placed on each of the fourteen time periods from the sixth to the forty-fifth postoperative days. Thus, there were eleven rats on every time interval, seven having fractured right fibulae and four being free from fractures. The controls served to adjudge the effect of the diet alone on the normal breaking strength of rat fibulae.

In the second paper of this series,<sup>1</sup> we determined the breaking strength of normal rat fibulae, in addition to the healing strength of fractured rat fibulae, in animals on a standard diet. The data obtained at that time are used throughout our present paper to evaluate the observed results. Relative metabolic studies on animal weight and food intake were again prepared, and representative roentgenograms of the healing fractures from interval to interval, as well as correlations between animal weight, fibular length and fibular strength, were made once more. Further, a gross examination of the callus was performed in an effort to add additional information to that obtained.

## RESULTS

To avoid confusion, the control and fracture groups are considered separately.

TABLE 1.—*Correlation Between the Fibular Length and the Fibular Strength for the High Carbohydrate Controls\**

	Fibular Length									
	2.0 Cm.		2.1 Cm.		2.2 Cm.		2.3 Cm.		2.4 Cm.	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Arithmetic mean.....	316	309	326	306	491	471	509	505	570	580
Combined arithmetic mean....	313		316		481		507		575	
Normal normal combined arithmetic mean .....	384		450		457		503		†	
Standard diet control combined arithmetic mean .....	303		303		394		526		482	
High fat diet control combined arithmetic mean.....	309		393		492		539		633	

\* Refer to table 1a for complete data.

† None of this length.

1. *The High Carbohydrate Controls.*—A. Correlation, (1) Between Fibular Length and Fibular Strength: The fibulae were divided into length groups as before,<sup>13</sup> and the respective breaking strengths of the right and left bones for each rat in each length group were placed under its particular division. It will be observed in table 1 that once more a positive correlation was obtained. Apparently, as the fibular length increases, the fibular strength likewise becomes greater.

(2) Between the Fibular Length and the Animal Weight: The fibular length divisions used previously were again utilized. The respective weight of each rat in the group was placed under each length division, and the arithmetic mean obtained for each division again indicated that the longer the animal's fibula the heavier the animal would be (table 2).



(3) Between the Weight of the Animal and the Length of Its Fibula: The arbitrary weight divisions used earlier in these studies<sup>13</sup> were again made use of, and the fibular breaking strength of each mem-

TABLE 2.—*Correlations Between the Fibular Length and the Animal Weight for the High Carbohydrate Controls\**

	Fibular Length				
	2.0 Cm.	2.1 Cm.	2.2 Cm.	2.3 Cm.	2.4 Cm.
Arithmetic mean .....	196	217	241	261	275
Normal normal arithmetic mean.....	209	230	251	284	†
Standard control arithmetic mean.....	214	223	233	278	295
High fat arithmetic mean.....	201	215	256	274	293

\* Refer to table 2a for complete data.

† None at this length.

TABLE 3.—*Correlation Between the Weight of the Animal and the Strength of Its Fibula for the High Carbohydrate Controls\**

	Weight Groups							
	190-225 Gm.		226-250 Gm.		251-275 Gm.		276-300 Gm.	
	Left	Right	Left	Right	Left	Right	Left	Right
Arithmetic mean.....	325	318	415	409	497	515	598	589
Combined arithmetic mean.....	322		412		506		589	
Normal normal combined arithmetic mean	401		415		498		564	
Standard diet control combined arithmetic mean .....	296		373		580		516	
High fat diet control combined arithmetic mean .....	332		443		481		589	

\* Refer to table 3a for complete data.

TABLE 4.—*Breaking Strength Ratios of High Carbohydrate Diet Controls\**

Postoperative Days Observed	Left Fibular Ratio	Right Fibular Ratio
6.....	205±11	219±8
9.....	230±33	235±35
12.....	232±18	257±13
15.....	289±20	274±16
18.....	269±38	286±42
21.....	232±17	222±25
24.....	242±29	238±37
27.....	190±3	165±17
30.....	175±16	185±21
33.....	200±21	173±22
36.....	178±18	173±17
39.....	269±48	270±53
42.....	257±10	269±10
45.....	210±35	201±14

\* Refer to table 4a for complete data.

ber in each division was recorded. It is evident from the means in table 3 that the heavier the animal the stronger is its fibula.

*B. Fibula Breaking Strength Ratios:* The breaking strength of the left and right fibulae of the four controls in each of the fourteen time

periods was determined as before.<sup>13</sup> Correction was then made by use of the formula  $R = \frac{F}{(10 \cdot W)^{2/3}}$ , and the results were tabulated in table 4, together with the standard deviation of the mean.

The left fibula was seen to be slightly stronger than the right, as it had been on the two diets studied before.<sup>13</sup> In figure 1 it will be noted that this difference is not constant, but over the duration of the experiment it is relatively so.

On the standard diet<sup>1</sup> it will be recalled that with the exception of a temporary rise above the normal breaking strength band on the twenty-fourth and twenty-seventh days, the strength diminished from

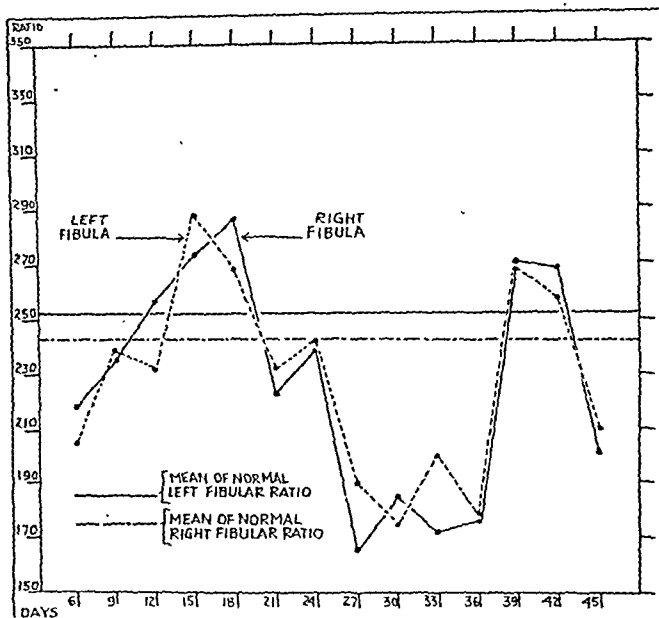


Fig. 1.—The breaking strength ratio of the left and right fibulae, with a normal ratio band. The high carbohydrate control group was entirely free from fractures. There was a slight increase in the strength of the fibulae during the early part of the experiment. Later strength was lost for a time, to be later regained and again lost. Strength was maintained somewhat better on this diet than on those described before. The left fibula was once more found to be stronger than the right.

the beginning to the end of the experiment in the control rats. The high fat diet controls, on the contrary, will be remembered to have shown wide fluctuations both above and below the normal band.<sup>2</sup> The trend of the breaking strength in the fat controls was, however, found to be slightly above normal. In the high carbohydrate control rats, as shown in figure 1, the breaking strength first increased, then diminished, again rose and again fell. The trend of the curve may be said to have been a primary rise followed closely by a secondary fall. Fibular strength in the control rats on the carbohydrate diet did not vary so sharply or

so frequently as it did on the fat diet, or so abruptly as on the standard. It did resemble the strength of the standard diet controls, though more in its tendency to decrease than to increase. Normal strength was probably better maintained on the high fat diet than on either the standard or the high carbohydrate diet.

C. Relative Data on Animal Weight and Food Ingestion: The animal weights fell from the onset of the experiment (table 5). This loss was not uniform, but the curve of weight in figure 2 is seen to drop throughout. Figure 2 also shows that somewhat the same loss in

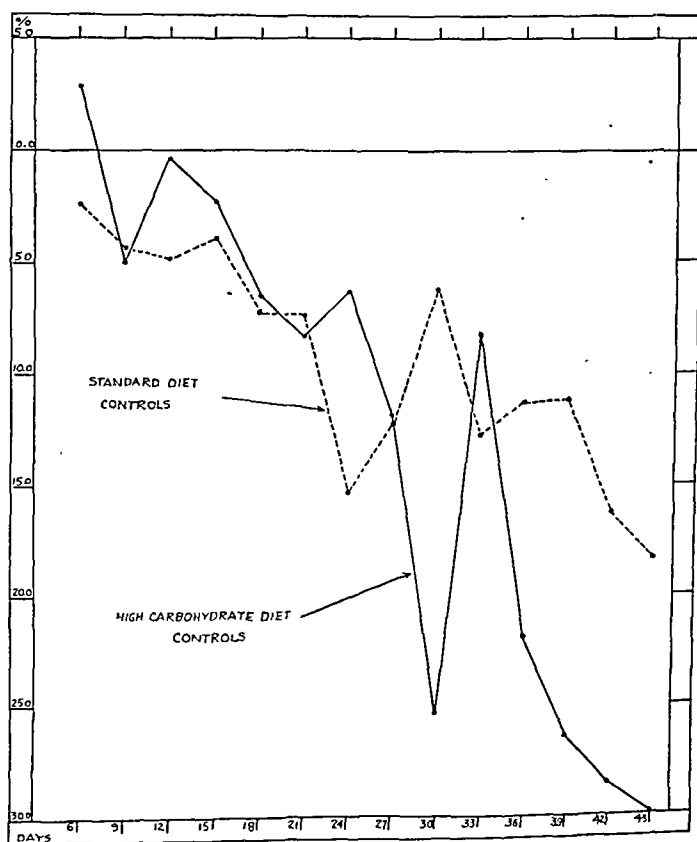


Fig. 2.—Difference in weight from operation to death, plotted as percentage of body weight at operation for the high carbohydrate and standard diet controls. The weight was at first comparatively well maintained on the high carbohydrate diet by the control animals, but later the rats were unable to reach the weights established by the standards on a standard diet.

weight occurred on the standard diet during the earlier part of the experiment. After the twenty-first day, however, the loss of weight was greater on the carbohydrate diet than it had been on the standard. Of the three diets so far reported, weight was more successfully maintained on the high fat diet<sup>2</sup> than it was on the standard or the high carbohydrate diet. Consequently, a greater loss occurred on the carbohydrate diet than on either the standard or the fat diet.

TABLE 5.—*Animal Weights and Food Intakes for the High Carbohydrate Controls\**

Postoperative Day	Difference in Weight from Operation to Sacrifice as Percentage of Weight at Operation	Food Consumed per Day from Operation to Sacrifice as Percentage of Weight at Operation
6.....	+ 2.9	9.2
9.....	— 5.1	6.7
12.....	— 0.4	5.5
15.....	— 2.2	4.7
18.....	— 6.5	5.8
21.....	— 8.2	6.2
24.....	— 6.3	5.9
27.....	—11.9	5.6
30.....	—25.1	4.9
33.....	— 8.1	5.3
36.....	—21.9	3.7
39.....	—26.2	3.6
42.....	—28.5	4.8
45.....	—30.0	4.5

\* Refer to table 5a for complete data.

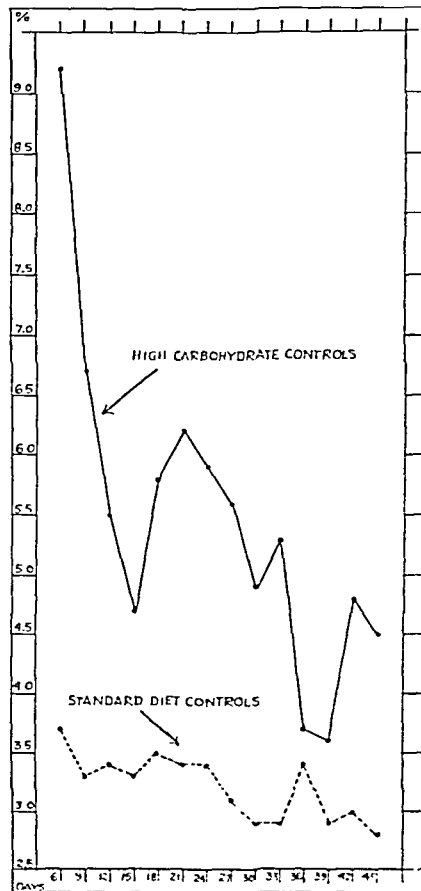


Fig. 3.—Food consumed per day, plotted as percentage of body weight at operation, for both the high carbohydrate and standard diet controls. The larger quantity of food consumed on the high carbohydrate diet is evident from the upper curve. Although the amount diminished over the extent of the experiment, it still remained higher than that eaten on the standard diet.

TABLE 6.—Calories Consumed per Day from Operation to Sacrifice by Control Rats on a Standard Diet, a High Carbohydrate Diet and a High Fat Diet

Postoperative Days	Standard Diet Controls	High Carbohydrate Diet Controls	High Fat Diet Controls
6.....	53.40	79.16	34.03
9.....	55.56	59.99	45.47
12.....	42.72	59.16	34.09
15.....	37.38	51.66	46.14
18.....	38.98	55.83	35.03
21.....	45.93	56.66	54.33
24.....	49.13	51.24	36.47
27.....	40.00	47.08	43.91
30.....	36.85	43.33	50.61
33.....	36.85	45.83	49.86
36.....	41.12	36.66	50.60
42.....	40.06	44.16	41.30
45.....	38.45	39.58	42.42

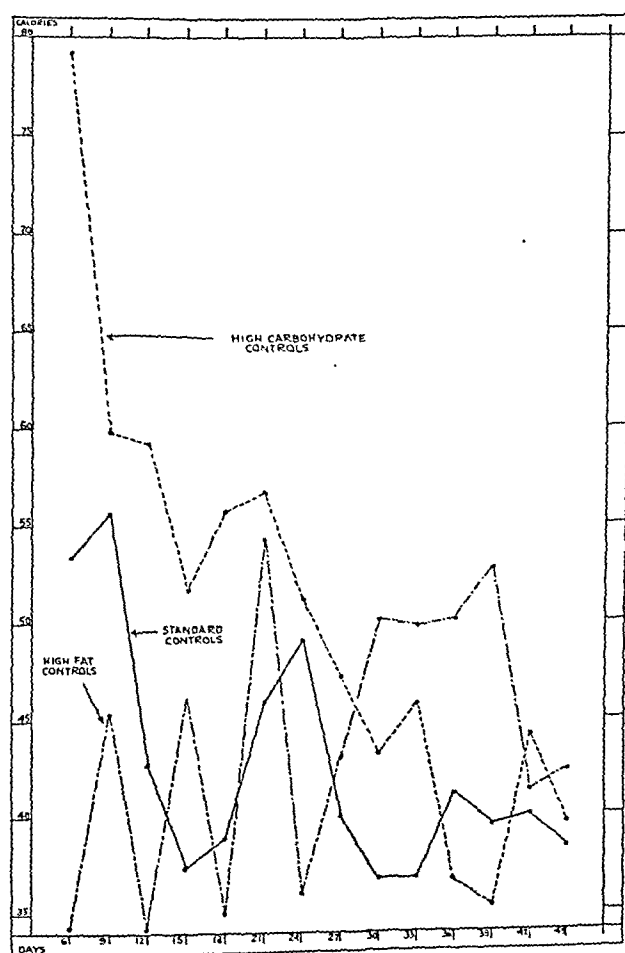


Fig. 4.—Calories consumed per day from operation to death by control rats free from fractures on a standard, a high fat and a high carbohydrate diet. The control animals consumed more calories on the high carbohydrate diet than on the standard or the high fat diet.

The quantity of food consumed on the high carbohydrate diet was greater than it had been on either the standard or the high fat diet. In figure 3 it is noted that although the amount taken by the animals fell after a short period of time, it nevertheless remained definitely more than on the standard diet. We have already observed<sup>2</sup> that on the high fat diet less food was eaten than on the standard, hence we are led to conclude that more of the carbohydrate diet was ingested by the animals than of either the standard or the high fat diet.

Calorically, the high carbohydrate diet afforded 4.166 calories per gram; the standard diet, 5.340 calories per gram, and the high fat diet, 7.442 calories per gram. The truth of Smith and Carey's<sup>16</sup> finding, that rats eat until their caloric demands are satisfied becomes evident when we consider our results on body weight and food intake. We saw that the quantity of the carbohydrate diet consumed was greater than that of either the standard or the high fat diet. The necessity for this is apparent when we note that the carbohydrate diet offers less calories per gram than does either of the other two diets.

The caloric intakes for the control animals on the three diets have been tabulated in table 6 and plotted in figure 4.

11. *High Carbohydrate Fracture Group.*—The left fibula in these animals was not fractured, while the right was fractured as before at a point opposite the tibial prominence.<sup>13</sup> Owing to the obvious differences between the two fibulae, their breaking strengths are considered separately.

A. *Unfractured Left Fibular Breaking Strength Ratio:* As in all previous studies, the breaking strength determinations were begun on the sixth and continued to the forty-fifth postoperative day.<sup>13</sup> A minimum of five observations was recorded for each of the fourteen time periods.

A rise in the ratio was noted on the twelfth day, which was three days earlier than a similar rise that occurred on the standard diet. The height reached was, however, about 90 lower than that found for the standard at its peak on the fifteenth day. An immediate fall in the ratio of the carbohydrate left fibula took place subsequent to the rise, as it had also done in the standard left. The low point reached by the carbohydrate on the fifteenth day was, however, 10 less than that attained by the standard on the twenty-first day. Thereafter, the ratio of the carbohydrate left fluctuated widely, but showed throughout a persistent reduction in its strength until by the forty-fifth day the ratio was 100 less than that observed for the standard on the same day. The ratios in table 7 have been plotted in figure 5.

TABLE 7.—*Breaking Strength Ratios of Unfractured Left and Fractured Right Fibulae on a High Carbohydrate Diet \**

Postoperative Day	Unfractured Left	Fractured Right
6.....	199± 6	12±10
9.....	208±32	76±19
12.....	243±28	102±12
15.....	182±17	107±19
18.....	201±32	101± 7
21.....	278±19	108±16
24.....	240±24	102±22
27.....	208±17	132±24
30.....	183± 9	151±14
33.....	222±26	142±11
36.....	175±13	115±14
39.....	157± 8	103±19
42.....	188±29	146±19
45.....	160±25	145±23

\* Refer to table 7a for complete data.

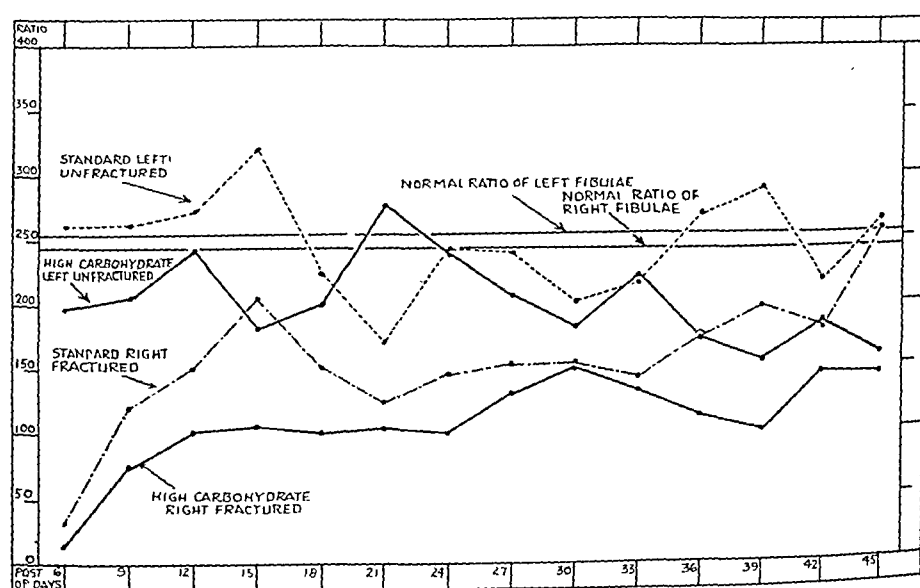


Fig. 5.—Ratio of healing strength of fractured right fibulae and breaking strength of unfractured left fibulae in high carbohydrate fracture group, with similar ratios for standard diet fibulae. The band represents the breaking strength ratios of fifty normal right and left fibulae. The primary callus was formed on the high carbohydrate diet by the fifteenth day as it had been on the standard diet. However, the subsequent drop due to the formation of the medullary space did not take place on the carbohydrate diet as it had on the standard diet. The unfractured left of the carbohydrate fractured group fluctuated in strength as the left of the standard diet did. This was thought to be due to the variable demands made on the left for salts with which to supply the fracture in the right fibula. The end-point was about 30 per cent lower than that attained by the standards.

*B. Fractured Right Fibular Ratio:* On the standard diet it was established that there are three particular points of interest on the curve of healing strength. These are the time at which the primary callus is formed, as shown by the first peak in the curve; the time at which the medullary space is formed, as shown by the sharp loss in strength subsequent to the formation of the primary callus, and the time taken to restore the strength of the fracture to that of the unfractured fibula on the opposite leg. In the standard diet we found the primary callus formed by the fifteenth day, the medullary space particularly active in its

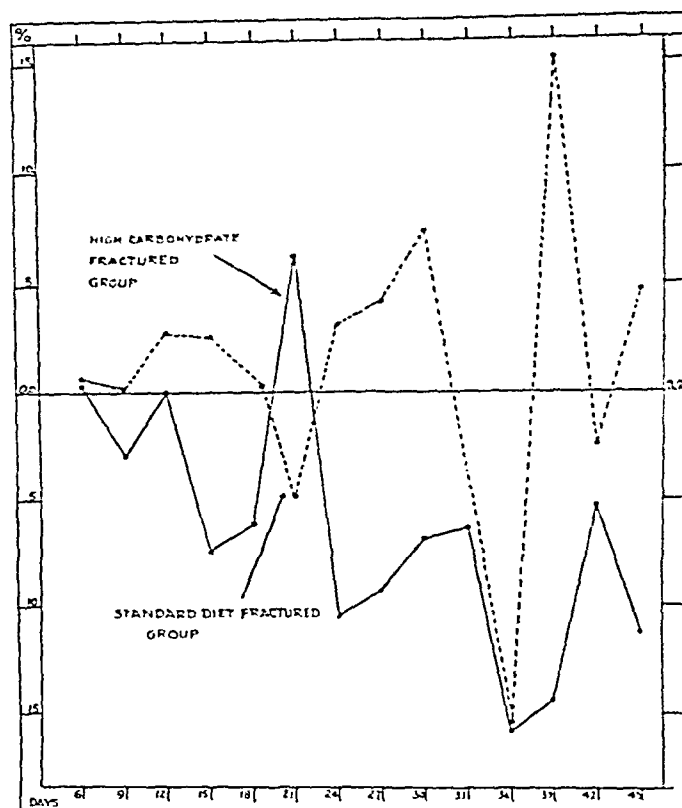


Fig. 6.—Difference in weight from operation to death, plotted as percentage of body weight at operation for the high carbohydrate and standard diet fractured groups. The high carbohydrate fractured group did not maintain the weight as successfully as did the standard fractured group. The early gain in weight during the first fifteen days on the standard diet, which was believed to be due to the increased metabolism as a result of the fracture, was not observed to occur on the high carbohydrate diet until twelve days later.

formation between the fifteenth and the twenty-first days and the end-point reached by the forty-fifth day.

In the carbohydrate diet the primary callus was also considered as having been formed by the fifteenth day, but it had a ratio 101 less than the standard and 5 less than the high fat on the same time period. The



fall noted to have occurred concomitantly with the gross appearance of the medullary cavity in the standard and the fat diets did not take place on the carbohydrate diet. On the contrary, it will be seen in table 7 and figure 5 that the ratio remained relatively constant from the fifteenth to the twenty-first day. This was within the time limits established by the standard diet, and three days later than that established by the high fat diet. The ratio for the carbohydrate fractured right on the forty-

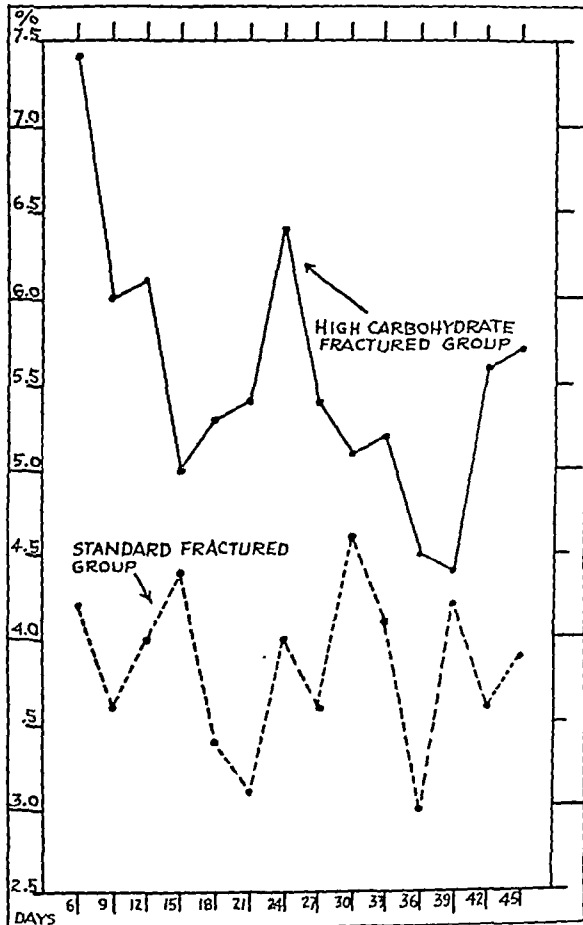


Fig. 7.—Food consumed per day, plotted as percentage of body weight at operation for both high carbohydrate and standard diet fractured groups. More food was consumed by the rats with fractured fibulae on a high carbohydrate diet than those on a standard diet.

fifth day was, however, 120 less than that for the standard right, and about 60 less than the high fat right.

C. Weight of Rats and Food Consumption: With the exception of a sharp rise on the twenty-first day, the weights fell from the beginning to the end of the experiment. The fall was not as rapid or as complete as it had been in the case of the carbohydrate controls, but it was more so than it had been in the standard fractures. A sugges-

tion of a moderate increase in body weight, in response to an acceleration of metabolism as a result of the injury induced by the fracture, may be noted in table 8 and figure 6. The weights of the rats remained in closer proximity to normal during that interval, and did not continue to fall until later.

The rats on a high carbohydrate diet with fractured fibulae consumed more food throughout than did the standards (table 8 and fig. 7). Despite this we have already seen that the weights of the animals fed carbohydrate decreased more than those of the standards. It was observed, as it had been before, that as the quantity of food consumed fluctuated, the weights of the animals did likewise. As one fell the

TABLE 8.—*Animal Weights and Food Intakes of Fractured Animals on a High Carbohydrate Diet \**

Postoperative Day	Difference in Weight from Operation to Sacrifice as Percentage of Weight at Operation	Food Consumed per Day from Operation to Sacrifice as Percentage of Weight at Operation
6.....	+ 0.4	7.4
9.....	— 3.0	6.0
12.....	0.0	6.1
15.....	— 7.5	5.0
18.....	— 6.1	5.3
21.....	+ 6.4	5.4
24.....	—10.5	6.4
27.....	— 9.3	5.4
30.....	— 6.9	5.1
33.....	— 6.4	5.2
36.....	—15.7	4.5
39.....	—14.4	4.4
42.....	— 5.2	5.6
45.....	—11.1	5.7

\* Refer to table 8a for complete data.

other also fell, and as the one rose, the other also rose. The diminution in the amount of food ingested and the loss in body weight of the rats may at least partially account for the loss in strength in the unfractured left fibula, for it was found earlier in this paper that body weight and fibular strength were positively correlated. It is conceivable that as weight was lost on the carbohydrate diet, the strength of the left fibula became less.

The calories consumed per day on the high carbohydrate diet would be expected to agree in the character of their plotted curve with the curve of the quantity of food consumed per day. Such proved to be the case. It may be seen in table 9 that the animals ate more calorically of the high carbohydrate diet than of either the standard or the high

fat diet. The curve for the carbohydrate calories in figure 8 is also at a consistently higher level than it is on the other two diets.

*D. Roentgenographic Studies:* The density of the callus increases to the twenty-fourth day, following which a moderate degree of rare-

TABLE 9.—*Caloric Intake per Day from Operation to Sacrifice for the Standard, the High Carbohydrate and the High Fat Fractured Animals*

Postoperative Day	Standard Diet Fractured Animals	High Carbohydrate Fractured Animals	High Fat Fractured Animals
6.....	23.37	30.83	23.51
9.....	19.22	24.99	14.66
12.....	21.36	25.41	20.34
15.....	23.50	20.83	20.24
18.....	18.16	22.07	24.55
21.....	16.55	22.49	22.10
24.....	21.36	26.66	19.50
27.....	19.22	22.49	18.30
30.....	24.56	21.25	17.63
33.....	21.89	21.66	16.24
36.....	16.02	18.75	20.46
39.....	22.43	18.33	18.60
42.....	19.22	23.33	26.04
45.....	20.83	23.75	20.24

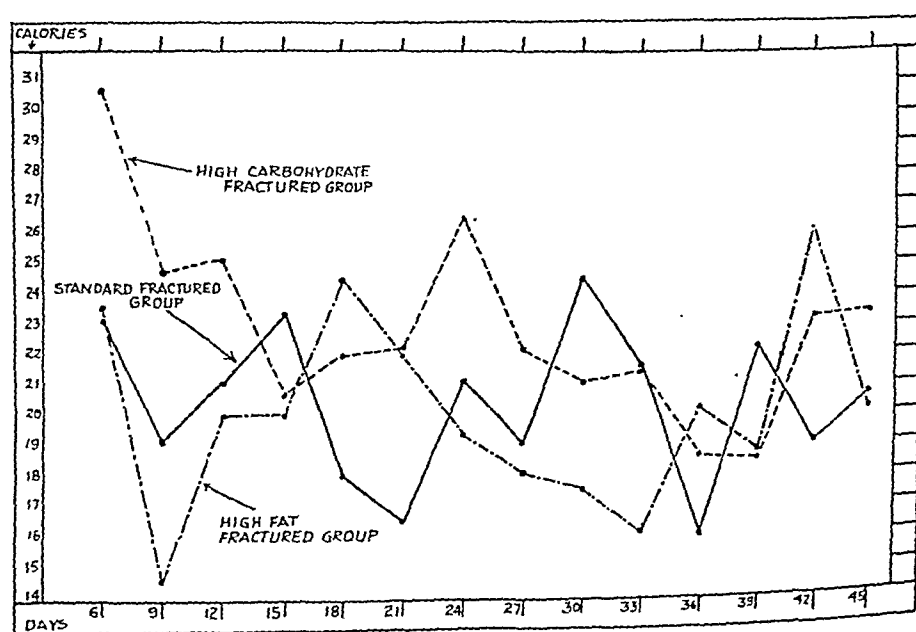


Fig. 8.—Caloric intake per day from operation to death for the standard, high carbohydrate and high fat fractured groups. In addition to eating more food, the high carbohydrate fractured animals ate more calories than on any diet previously studied.

fraction becomes evident (fig. 9). The formation of the medullary space, suggested on the standard and fat diets by a reduction in the density between the fifteenth and the twenty-first days, was not so clearly seen in the carbohydrate fractures. Subsequent to the thirtieth day, the size of the callus was much less than it had been in the standard fractures, and this may at least partially explain the lowered strength apparent in it at that time. The reorganization of the bony contour of the diaphysis is well shown in figure 9, as is the reduction in its size. By the time the end-point had been reached on the forty-fifth day, the shaft

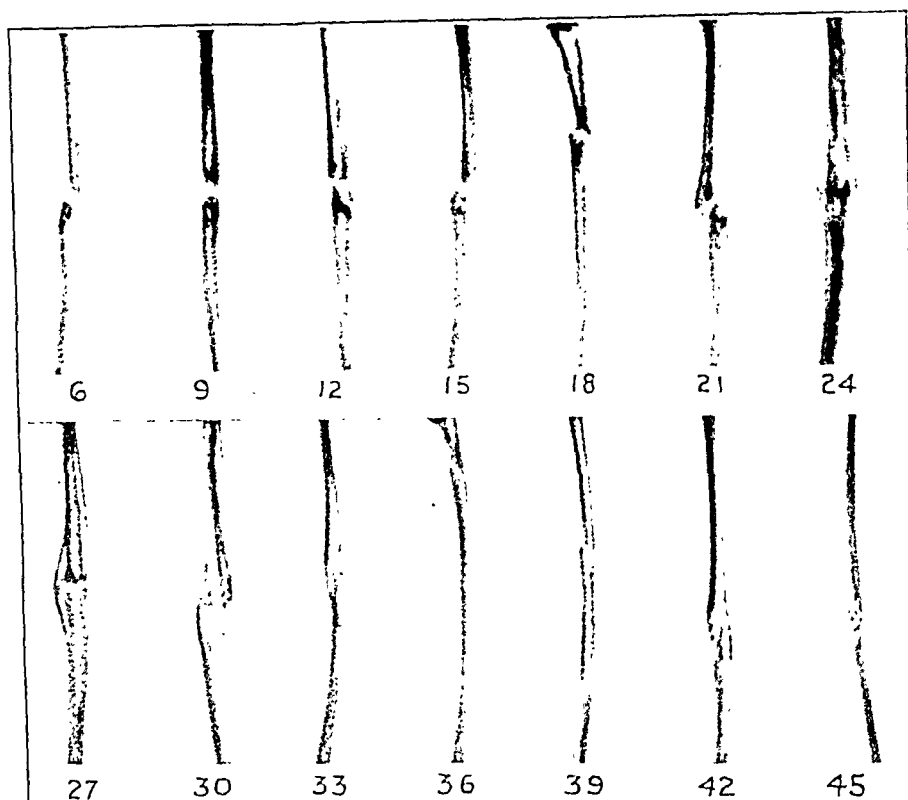


Fig. 9.—The roentgenograms taken of representative fractures in the high carbohydrate fracture group in each of the fourteen time periods studied again demonstrated the inaccuracy of attempts to correlate healing strength with the roentgenographic picture. Strength from the fifteenth day on changed but little, yet the image noted in the roentgenograms varied a great deal. The soft and proliferating tissue between the fracture ends does not appear in the roentgenograms unless calcified, but it possesses, nevertheless, a high degree of breaking strength;  $\times 3\frac{1}{2}$ .

of the fibula was a mere splinter, and one can readily understand its low strength ratio.

*E. Gross Examination of the Callus:* After the breaking strength determinations had been made, the separated proximal and distal fragments were mounted in blackened corks in such a manner that the calluses could be examined end-on beneath a dissecting microscope.

The delayed formation of the primary callus was evident at once, as was the retarded appearance of the medullary space. The diameter of the callus was observed to be below normal; the diameter of the medullary space was reduced, and the cortex was relatively thicker throughout than it had been in the standard calluses. Apparently the factors going to form the medullary space were less active on the carbohydrate diet. The histologic studies, in course of preparation, should aid our interpretation of the cytologic reaction of the healing fractures to the high carbohydrate diet.

#### COMMENT

For the third time it has been possible to demonstrate correlations between animal weight, fibular length and fibular breaking strength on the control animals. For the present, at least, we are apparently able to accept these correlations *in toto*.

If we may judge the efficiency of the diet on the basis of the breaking strength of the control rat fibula, we are led to believe that the high carbohydrate diet produces the greatest loss in fibular strength, while the high fat diet produces the least and the standard diet adopts an intermediate point. The diets were originally calculated by Moise and Smith,<sup>14</sup> from work previously done by Smith and Carey,<sup>15</sup> in such a manner that, although the quantity of food eaten by the rats differed with the diet offered, the salt intake would be essentially the same for each. Consequently we are not entirely justified in assuming that the variations from the normal breaking strength observed in the carbohydrate controls are due to differences in salt intake. Rather, we must consider, among other things, the possibility of an increase in the absorption of carbohydrate being followed by a reduction in the phosphates of the blood stream. Such a condition may result in an increase in the excretion of calcium to compensate for the reduction in available phosphates; it may diminish the quantity of phosphates suitable for repair of bone by putting them in such a form that they are not utilizable, or, on the contrary, it may even increase the available phosphates and reduce the quantity or activity of the bone esterase phosphatase. Studies on blood chemistry in connection with these diets are to be published at a later date, and will, it is hoped, add to our knowledge of the factors concerned in the loss of fibular strength in normal control rats on a high carbohydrate diet.

In the fibulae with fractures, the healing strength did not attain the level reached by either the high fat or the standard diet fractures on the fifteenth day. It did, however, show its first peak at that time, and this was interpreted as evidence that the provisional callus had formed within the normal time limit. The loss in strength immediately following the fifteenth day, seen in former dietary studies and attributed to the

rapid development of the medullary space during that interval, did not occur on the carbohydrate diet. Subsequently, the strength of the fracture on the carbohydrate diet became only slightly greater, and, in fact, reached an end-point on the forty-fifth postoperative day with a ratio of healing strength only 40 above that reached by its primary callus on the fifteenth day. The fracture healed in the time limits set by the standard diet fractures, but it did so at the expense of the strength of the unfractured left fibula.

The unfractured left fibula, in rats on a high carbohydrate diet with fractured right fibulae, increased slightly in strength during the first part of the experiment. This was thought to be due to a systemic increase in the metabolic elements creating bone strength. Among them we considered phosphatase as a possibility. Phosphatase occurs in the serum and bone in amounts above normal during the early stage of fracture healing,<sup>17</sup> and may explain the increased strength in the left fibula through the stage of primary callus formation. The lower height reached by the left fibula on the carbohydrate diet, as compared with the greater height reached by the left fibula on the standard diet, might be considered as additional evidence of either a diminution in the available phosphates; the presence of phosphates in normal amounts, but in a form on which phosphatase cannot act, or as a reduction in the phosphatase itself. Suffice it to say at this time that the strength of the left fibula varies after the provisional callus has been formed in proportion to the demands made on it by the healing fractured right fibula.

In no respect have we attempted to make detailed studies of the metabolism of the rats on the different diets. Rather, our prime consideration has been the effect of the diet on the healing strength of the fibula. However, several interesting features have developed in the studies we have made.

We have observed in the control animals free from fracture that the heavier the rat the stronger its fibula. Along the same line it was seen in the fracture animals that, within certain limitations, the strength of the fibula became greater as the weight of the rat increased, and fell as the weight diminished. It is quite true that this was but one of the many factors concerned in the reparative process, but it is nevertheless one of some importance. Healing of the fractured right fibula was completed within the time limits established on the standard diet, but was completed at the expense of the unfractured left fibula. Coincidentally, body weight dropped even as the strength of the unfractured left fibula became less. It would appear not unreasonable that part of the loss in strength of the left fibula was due to the presence of some inhibitory substance in the diet resulting in the inability of the left fibula to maintain its normal strength in the face of demands for healing

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17. Kay, H. D.: *J. Biol. Chem.* **99**:249, 1930.

substances being made on it by the fractured right, or, on the other hand, its diminishing strength may have been due to a lack of some substance in the diet which was necessary for the repair of the fracture and which could be furnished only by the left fibula. Body weight and food intake are seemingly better indexes of the progress of the healing of fractures than we have previously believed.

The roentgenographic studies, although the interpretations that we are enabled to put on them are purely relative, are still of value. They afford a basis on which to estimate, somewhat roughly it is true, the degree or extent of the calcific process at any given time. They do not, however, show the organic material present about the callus, and it is this material with which we find ourselves chiefly concerned in the earlier stages of repair. An appreciable strength has been found in callus formed primarily of fibrous tissue which roentgenograms had previously led us to believe would have little if any strength. The roentgenogram has also been found to be an unsatisfactory method for determining the appearance of the medullary space, and for showing details of cortical thickening and reorganization. Possibly a more highly developed technic would obviate the difficulties that have arisen in connection with our use of the x-rays, but we are of the opinion at this time that they afford at best only a very relative index of callus strength and the course of the reparative process.

#### SUMMARY

1. Correlations on control rats, free from fractures, on a high carbohydrate diet have shown that on an average the heavier the animal, the longer and stronger its fibula will be. The reverse was also found to be true.

2. The breaking strength of the fibulae of the carbohydrate control rats was less than that of either the standard or the high fat diet control animals.

3. The breaking strength of the left fibulae in the carbohydrate controls was slightly greater than that of the right fibulae.

4. Body weight was maintained in the carbohydrate controls during the first twenty-one days at a level at least equal to that observed in the standard diet controls. Subsequently, the carbohydrate controls lost more weight than the standards.

5. The quantity of food consumed per day, as well as the calories consumed per day, by the carbohydrate control rats was uniformly greater than that ingested by either the standard or the high fat diet control animals.

6. In the animals on a high carbohydrate diet with fractured right fibulae, the primary callus was formed by the fifteenth day, but possessed less strength than did the calluses of the standard and the high fat fractures observed at the same interval.

7. The sharp drop in strength noted after the fifteenth day in the standard and the high fat fractures, which was believed to be due to the appearance of the medullary space, did not occur on the high carbohydrate diet. Grossly, it was seen that the medullary space was less completely formed and the cortex of the shaft was relatively thicker during the time medullary cavitation should have been developing, in the calluses of rats on a carbohydrate diet, than it had been in the calluses of rats on either the standard or the high fat diet.

8. The end-point was reached by the healing fracture on the carbohydrate diet by the forty-fifth day, which was within the limits established by the standard diet. Strength was, however, definitely less than on the standard or the high fat diet.

9. The unfractured left fibulae of rats on a high carbohydrate diet where the right fibula had been fractured, first increased in strength and then diminished, until by the forty-fifth day the strength was considerably lower than it had been in the case of the left fibulae of rats on a standard diet. The early rise in the left fibular strength was believed to be associated with the formation of the provisional callus in the fractured fibula of the opposite leg, and it was thought that the simultaneous variations in the curves of the left unfractured fibula alone indicated the repair of fractures to be a generalized phenomenon, and not one purely local in character. Thereafter, the loss in strength in the left fibula was possibly due to demands made on its constituents of strength in an effort to meet the lack of essential substances in the diet necessary for the repair of the fracture in the right fibula, or to overcome the presence of dietary products inhibitory to the successful healing of the fracture.

10. Roentgenographic studies of representative calluses over the course of the investigation indicated once more that x-rays afford an unsatisfactory means by which to determine callus strength at any given interval, or with which to obtain detailed knowledge of the stages of healing in the fracture.

#### CONCLUSIONS

A high carbohydrate diet, in which the protein and the salt requirements were satisfied, was fed rats with healing fractured right fibulae. Determinations of the breaking strength of the calluses were made at intervals of three days. The primary callus was observed to form within the normal limit of fifteen days, but it was seen to possess less strength than did calluses of animals on standard and high fat diets. The normal loss in strength occurring immediately after the formation of the provisional callus and held to be due to the formation of the medullary space was not noted in rats on the carbohydrate diet. The end-point was reached on the forty-fifth day, which was within the



normal time limit. Strength was, however, less than in either the standard or the high fat diet fractures at the same interval.

The strength of unfractured left fibulae, in the animals with fractured right fibulae, increased to the twelfth day as the primary callus was forming in the opposite fibulae. It fluctuated subsequently and ended on the forty-fifth day at a point lower than that of the unfractured left fibula in animals on standard and on high fat diets. The progressive loss in strength was considered as being due to an attempt to meet the demands of the healing fracture. This may be taken to indicate that the diet was unsatisfactory in any one or more of several ways.

In control rats free from fractures on the same diet for the same period of time, fibular strength first increased and then diminished. On an average, the strength of these control fibulae was less than similar controls on standard and high fat diets.

The body weight of both the control and the fractured animals on the high carbohydrate diet was less than that for similar control and fractured rats on standard and high fat diets. The quantity of food and the caloric intake were, however, somewhat greater.

The possible relation of hexose and glycerophosphates to phosphatase has been briefly considered. The question of the antagonism between phosphatase and the hormone of the parathyroid gland has been considered elsewhere.<sup>13</sup>

## ADDENDA

### COMPLETE DATA FOR HIGH CARBOHYDRATE DIET

TABLE 1a.—*Correlation Between Fibular Length and Fibular Strength for High Carbohydrate Control Group*

	2 Cm.		2.1 Cm.		2.2 Cm.		2.3 Cm.		2.4 Cm.	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
	300	375	225	225	425	380	505	450	350	415
	500	515	375	380	375	365	360	375	610	625
	415	400	350	390	465	525	405	450	755	775
	225	200	425	450	590	430	475	510	435	410
	310	330	260	300	505	460	475	560	670	675
	295	215	245	250	530	490	425	515	...	...
	275	290	240	260	560	640	405	360	...	...
	350	360	505	525	480	475	470	430	...	...
	430	460	365	375	...	...	705	600	...	...
	300	335	310	225	...	...	700	710	...	...
	410	365	200	275	...	...	635	505	...	...
	350	370	225	230	...	...	550	600	...	...
	300	350	360	340	...	...	...	...	...	...
	200	180	310	385	...	...	...	...	...	...
	310	305	310	380	...	...	...	...	...	...
	305	245	395	410	...	...	...	...	...	...
	450	460	390	315	...	...	...	...	...	...
	205	175	...	...	...	...	...	...	...	...
	315	260	...	...	...	...	...	...	...	...
	170	200	...	...	...	...	...	...	...	...
	295	200	...	...	...	...	...	...	...	...
	250	200	...	...	...	...	...	...	...	...
Arithmetic mean	316	309	326	306	491	471	509	505	570	550
Combined arithmetic mean....	313		316		491		507		575	

TABLE 2a.—*Correlation Between Fibular Length and Animal Weight for High Carbohydrate Control Group*

2 Cm.	2.1 Cm.	2.2 Cm.	2.3 Cm.	2.4 Cm.
190	199	202	228	234
190	199	208	235	265
190	198	240	242	275
190	198	243	242	285
190	202	248	256	295
190	205	250	265	...
190	205	255	270	...
194	214	280	272	...
195	216	...	272	...
195	218	...	280	...
195	218	...	282	...
196	225	...	295	...
196	233	...	...	...
197	233	...	...	...
198	240	...	...	...
198	245	...	...	...
200	258	...	...	...
202	...	...	...	...
204	...	...	...	...
205	...	...	...	...
210	...	...	...	...
210	...	...	...	...
196	217	241	261	275

TABLE 3a.—*Correlation Between Animal Weight and Fibular Strength for High Carbohydrate Control Group*

190-225 Gm.		226-250 Gm.		251-275 Gm.		276-300 Gm.	
Left	Right	Left	Right	Left	Right	Left	Right
415	400	275	155	380	415	435	410
500	515	360	340	560	640	670	675
300	375	360	375	475	560	550	600
225	225	310	385	390	315	700	710
275	290	310	380	425	515	635	505
225	200	465	525	610	625	...	...
375	380	475	510	405	360	...	...
310	330	405	450	470	430	...	...
295	215	590	430	755	775	...	...
350	360	395	410	...	...	...	...
430	460	505	460	...	...	...	...
300	335	530	490	...	...	...	...
410	365	...	...	...	...	...	...
350	370	...	...	...	...	...	...
300	250	...	...	...	...	...	...
200	180	...	...	...	...	...	...
425	450	...	...	...	...	...	...
350	390	...	...	...	...	...	...
305	245	...	...	...	...	...	...
310	305	...	...	...	...	...	...
450	460	...	...	...	...	...	...
425	380	...	...	...	...	...	...
205	175	...	...	...	...	...	...
260	300	...	...	...	...	...	...
315	260	...	...	...	...	...	...
240	260	...	...	...	...	...	...
245	250	...	...	...	...	...	...
375	365	...	...	...	...	...	...
250	200	...	...	...	...	...	...
295	200	...	...	...	...	...	...
505	525	...	...	...	...	...	...
365	375	...	...	...	...	...	...
310	225	...	...	...	...	...	...
260	275	...	...	...	...	...	...
225	230	...	...	...	...	...	...
325	318	415	409	497	515	598	580
322		412		506		589	

TABLE 4a.—*Force and Ratio for High Carbohydrate Control Group*

Post-operative Days	Rat Number	Weight (W)		Force (F)		Ratio (R)	
		At Operation	To (10.W) <sup>2/3</sup>	Left	Right	Left	Right
6	2730	194	155.6	350	360	225	231
	2731	195	157.7	310	305	197	193
	2732	235	178.3	310	335	174	216
	2733	196	156.6	350	370	224	236
Arithmetic mean with standard deviation		207				205±11	210±8
9	2726	190	153.4	415	400	270	261
	2727	270	193.9	405	360	209	186
	2728	205	161.4	245	230	152	155
	2729	190	153.4	500	515	326	336
		214				239±33	235±35
12	2722	295	205.7	550	600	267	292
	2723	272	194.9	470	430	241	221
	2724	265	191.5	425	515	222	269
	2725	190	153.4	300	375	196	244
		256				232±13	257±13
15	2718	250	184.2	530	490	288	266
	2719	295	205.7	670	675	326	328
	2720	242	180.3	405	450	225	250
	2721	282	199.6	635	505	318	253
		267				289±20	274±16
18	2714	255	186.7	560	640	300	343
	2715	280	198.6	700	710	353	358
	2716	190	153.4	225	225	147	147
	2717	195	156.1	430	460	275	296
		230				269±38	286±42
21	2678	242	180.3	475	510	263	263
	2679	202	159.8	425	380	266	238
	2680	235	176.8	360	375	204	212
	2847	198	157.7	305	245	193	155
		219				232±17	222±23
24	2674	214	166.1	505	525	304	316
	2676	200	158.8	450	460	283	290
	2677	208	162.9	375	365	230	224
	2846	210	164.0	250	200	152	122
		208				242±20	238±37
27	2661	196	156.6	300	250	192	160
	2662	204	160.9	315	260	196	162
	2663	195	156.1	300	335	192	215
	2736	210	164.0	295	200	180	122
		201				190±3	165±17
30	2656	216	167.1	365	375	218	224
	2657	240	179.3	310	380	173	212
	2658	190	153.4	275	290	180	190
	2734	197	137.2	200	180	127	115
		211				175±16	185±21
33	2652	218	168.1	310	225	185	134
	2653	190	153.4	225	200	147	130
	2654	235	176.8	360	340	204	192
	2655	195	156.1	410	365	263	234
		210				200±21	173±22
36	2352	238	188.1	390	315	207	168
	2353	225	171.7	225	230	131	124
	2354	218	168.1	260	275	155	164
	2355	245	181.7	395	410	217	226
		237				178±18	173±17
39	2349	190	153.4	375	350	244	245
	2350	202	159.8	205	175	128	110
	2351	265	191.5	610	625	318	326
	2356	275	196.3	755	775	385	395
		233				269±48	270±33
42	2648	248	183.2	505	460	276	251
	2649	240	179.3	465	525	259	262
	2650	198	157.7	350	290	222	245
	2651	195	157.7	425	450	269	256
		221				257±10	242±10
45	2644	243	180.8	500	430	326	258
	2645	202	159.8	260	200	163	155
	2646	190	153.4	310	230	202	215
	2647	205	161.4	240	260	149	161
		210				216±25	201±14

TABLE 5a.—*Weight and Food for High Carbohydrate Control Group*

Post-operative Days	Rat Number	Weight			Food Consumed	
		Start	Operation	Death	Start to Operation	Operation to Death
6	2730	200	194	200	99	83
	2731	215	198	210	88	178
	2732	240	238	236	140	110
	2733	222	196	205	87	83
Arithmetic mean.....		219	207	213	104	114
9	2726	190	190	172	86	86
	2727	275	270	273	82	155
	2728	210	205	205	91	143
	2729	190	190	160	98	136
		216	214	203	89	130
12	2722	300	295	310	104	169
	2723	280	272	245	93	163
	2724	265	265	275	105	163
	2725	210	190	190	109	183
		264	256	255	103	170
15	2718	250	250	230	191	239
	2719	295	295	278	93	171
	2720	230	242	248	95	157
	2721	280	282	288	95	176
		264	267	261	119	186
18	2714	260	255	254	102	215
	2715	298	280	265	...	...
	2716	198	190	152	100	231
	2717	210	195	190	100	278
		242	230	215	101	241
21	2678	254	242	223	144	274
	2679	218	202	198	120	355
	2680	248	235	232	120	319
	2847	190	198	152	128	190
		228	210	201	128	285
24	2674	224	214	210	80	277
	2676	202	200	171	119	298
	2677	214	208	202	131	330
	2846	195	210	196	92	277
		209	208	195	106	296
27	2661	195	196	150	43	308
	2662	232	204	193	42	312
	2663	212	195	176	48	279
	2736	225	210	190	58	322
		216	201	177	48	305
30	2656	240	216	147	59	303
	2657	250	240	166	160	346
	2658	195	190	147	64	351
	2734	200	197	171	76	246
		221	211	158	75	312
33	2652	230	218	218	86	433
	2653	198	190	173	35	374
	2654	262	235	192	42	297
	2655	220	195	190	52	363
		228	210	193	54	367
36	2352	250	258	206	98	297
	2353	212	225	144	108	335
	2354	222	218	190	104	311
	2355	238	245	200	102	315
		231	237	185	103	315
39	2349	190	190	148	85	280
	2350	200	202	150	95	313
	2351	262	265	190	120	391
	2356	270	275	198	118	342
		231	233	172	105	332

TABLE 5a.—*Weight and Food for High Carbohydrate Control Group—Continued*

Post-operative Days	Rat Number	Weight			Food Consumed	
		Start	Operation	Death	Start to Operation	Operation to Death
42	2648	248	248	146	70	410
	2649	258	240	164	71	512
	2650	210	198	160	60	468
	2651	200	198	160	84	391
		229	221	158	71	445
45	2644	250	243	140	62	435
	2645	215	202	138	86	425
	2646	200	190	163	52	447
	2647	230	205	145	45	407
		224	210	147	61	429

TABLE 7a.—*Force and Ratio for High Carbohydrate Diet Fractured Group*

Post-operative Days	Rat Number	Weight (W)		Force (F)		Ratio (R)	
		At Operation	To (10.W) <sup>2/3</sup>	Left	Right	Left	Right
6	2059	270	193.9	365	0	188	0
	2060	223	170.7	355	0	226	0
	2061	227	172.7	340	95	196	55
	2062	240	179.3	335	0	187	0
	2063	265	191.5	375	15	196	7
Arithmetic mean with standard deviation mean.....						190±6	12±10
9	2052	275	196.8	480	105	245	54
	2055	200	158.8	290	170	183	108
	3328	232	175.2	425	45	243	26
	3329	220	169.1	605	190	358	116
						208±32	76±19
12	2042	245	181.7	250	130	138	72
	2043	272	194.9	550	235	282	131
	2044	258	188.1	480	160	255	85
	2045	276	196.8	625	265	318	135
	2048	190	153.4	340	135	222	88
						243±28	102±12
15	2036	198	157.7	230	95	146	60
	2037	190	153.4	375	85	244	55
	2041	245	181.7	265	140	146	77
	3118	194	155.6	350	265	225	170
	3119	190	153.4	220	240	144	157
	3117	190	153.4	290	185	189	121
						182±17	107±19
18	2031	250	184.2	240	150	130	81
	2032	198	157.7	220	140	139	89
	2034	285	201.0	430	240	214	119
	2670	270	193.9	630	180	325	93
	2671	190	153.4	300	185	196	121
						201±32	101±7
21	3335	252	185.2	525	185	283	100
	3332	190	153.4	375	240	244	156
	3331	190	153.4	340	150	221	98
	3333	220	169.1	580	140	343	83
	3334	240	179.3	555	190	310	106
						278±19	108±16
24	2011	194	155.6	275	185	177	119
	2066	280	198.6	560	350	282	176
	2060	260	189.1	405	220	214	116
	2667	272	194.9	395	90	203	46
	2672	228	173.2	560	90	323	52
						240±24	102±22
27	1999	190	153.4	320	205	200	134
	2002	265	191.5	405	170	211	89
	2003	272	194.9	525	360	269	185
	2005	254	186.2	275	105	148	56
	2067	250	184.2	370	260	201	195
						208±17	102±24

TABLE 7a.—*Force and Ratio for High Carbohydrate Diet Fractured Group*  
—Continued

Post-operative Days	Rat Number	Weight (W)		Force (F)		Ratio (R)	
		At Operation	To (10.W) <sup>2/3</sup>	Left	Right	Left	Right
30	2013	255	186.7	390	345	209	184
	2015	280	198.6	350	190	177	96
	2016	200	158.8	280	275	176	173
	2018	205	161.4	250	225	155	139
	2830	285	201.0	400	325	199	162
						183±9	151±14
33	1982	252	185.2	390	335	211	181
	1985	202	159.8	360	200	225	125
	1987	209	158.8	...	255	...	161
	2665	213	165.6	530	235	320	142
	2852	192	154.4	225	170	146	110
	2851	260	189.1	390	250	206	132
						222±26	142±11
36	1980	222	170.2	310	130	182	76
	1981	190	153.4	270	210	176	137
	1983	255	186.7	250	205	134	110
	1986	275	196.3	440	320	224	163
	2853	232	175.2	275	155	157	88
						175±13	115±14
39	1993	296	206.2	300	240	145	117
	1995	198	157.7	220	80	139	51
	1996	262	190.1	350	160	184	84
	1997	200	158.8	230	275	145	173
	1998	260	189.1	325	175	172	93
						157±8	103±19
42	1968	210	164.0	200	190	122	116
	1969	212	165.0	315	240	191	146
	1970	220	169.1	510	380	302	225
	1971	200	158.8	180	160	113	101
	1972	225	171.7	360	245	209	143
						188±29	146±19
45	1962	209	163.5	225	190	138	116
	1963	238	178.3	175	200	98	112
	1965	228	173.2	200	195	115	113
	1966	248	183.2	415	450	227	246
	1967	252	185.2	410	255	221	138
						160±25	145±23

TABLE 8a.—*Weight and Food for High Carbohydrate Fracture Group*

Post-operative Days	Rat Number	Weight			Food Consumed	
		Start	Operation	Death	Start to Operation	Operation to Death
6	2059	274	270	255	110	119
	2060	228	223	220	101	94
	2061	219	227	232	87	100
	2062	245	240	238	117	87
	2063	292	265	282	116	143
Arithmetic mean.....		252	245	246	106	109
9	2052	268	275	280	179	176
	2055	200	200	195	78	107
	3328	220	232	220	90	102
	3329	205	220	205	105	112
		223	232	225	113	124
12	2042	230	245	222	112	154
	2043	278	272	268	143	222
	2044	262	258	256	118	199
	2045	280	276	290	102	185
	2048	190	190	195	110	162
	2065	266	255	263	114	178
		251	249	249	118	183

TABLE 8a.—*Weight and Food for High Carbohydrate Fracture Group—Continued*

Post-operative Days	Rat Number	Weight			Food Consumed	
		Start	Operation	Death	Start to Operation	Operation to Death
15	2036	198	198	205	98	137
	2037	190	190	192	105	179
	2041	245	245	240	113	194
	3118	200	194	165	88	158
	3119	190	190	164	70	122
	3117	190	190	150	82	117
		202	201	186	93	151
18	2031	245	250	238	119	191
	2032	198	198	189	110	224
	2033	238	190	172	80	185
	2034	285	285	275	90	214
	2670	268	270	255	102	315
	2671	202	190	175	58	197
		239	231	217	93	221
21	3331	190	190	154	90	252
	3332	195	190	165	68	200
	3333	232	220	205	92	257
	3334	255	240	218	95	270
	3335	260	252	186	98	253
		226	218	232	89	246
24	2011	195	194	195	75	218
	2066	300	280	295	110	335
	2660	255	260	193	...	219
	2667	280	272	248	...	...
	2672	218	228	172	95	245
		250	247	221	93	254
27	1999	196	190	192	84	373
	2002	272	265	235	116	320
	2003	260	272	220	125	291
	2005	262	254	230	161	509
	2067	245	250	230	125	310
		251	246	223	122	361
30	2031	240	255	248	153	420
	2015	254	280	230	88	378
	2850	288	285	248	182	430
	2016	195	200	195	73	321
	2018	216	205	220	81	312
		239	245	228	115	372
33	2852	190	192	173	...	367
	1982	290	252	262	100	494
	1985	225	202	200	...	...
	1987	193	200	195	60	294
	2665	242	213	180	62	392
	2851	245	260	225	126	394
		232	220	206	87	376
36	2853	220	232	215	54	374
	1980	220	222	198	100	368
	1981	200	190	180	100	352
	1983	280	255	180	60	382
	1986	295	275	215	90	393
		243	235	198	81	350
39	1993	300	296	270	105	397
	1995	205	198	180	91	330
	1996	276	262	205	100	402
	1997	215	200	180	96	463
	1998	258	260	205	90	501
		251	243	208	97	419
42	1968	208	210	177	95	420
	1969	220	212	205	97	564
	1970	210	220	240	101	523
	1971	208	200	185	96	575
	1972	234	225	206	83	512
		216	213	202	95	499
45	1962	232	209	180	102	619
	1963	251	238	177	92	540
	1965	220	228	202	109	570
	1966	242	248	242	116	709
	1967	252	252	243	98	605
		239	235	209	103	609

## ETIOLOGY OF FEMORAL HERNIA

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Are femoral hernial sacs of congenital or acquired origin? The answer to this question should be of interest to students of anatomy and embryology and to biologists in general, and of even greater interest and real practical importance to surgeons. If these sacs are always congenital, then simple extirpation of the peritoneal diverticulum would hold out promise of cure to patients afflicted with this condition. If, on the other hand, all are acquired, then removal of the sac alone will not be sufficient, and other factors concerned in the process must be corrected before a lasting repair can be obtained.

In order to study the factors that may have a bearing on this problem, two different types of observations were made. The first consisted of clinical material, that is, all femoral hernias seen at the University Hospital; the second, of anatomic dissections and measurements.

All femoral hernias, with the exception of a rare type that passes directly through the lacunar ligament (Gimbernat's), go through the lacuna vasorum. The latter (fig. 1) is an almost oval space lying under Poupart's ligament and separated from the lacuna musculorum by a strip of fascia, the iliopectineal ligament. The lacuna vasorum is bounded anteriorly by Poupart's ligament, posteriorly by the pubis covered by the pectineous muscle and Cooper's ligament, internally by Gimbernat's ligament and externally by the iliopsoas muscle covered by the iliopectineal ligament. The structures that pass through the lacuna vasorum are the femoral artery and vein, the crural branch of the genitocrural nerve and the femoral canal. The femoral ring lies between the femoral vein and Gimbernat's ligament. It is separated from the peritoneal cavity by the septum crurale. The femoral canal contains a few lymphatic vessels, some fat and frequently a lymph gland known as Rosenmueller's gland.

Accurate measurements of the femoral ring itself are impossible because of its variable lateral wall consisting of the easily collapsable femoral vein. Panton has been the only one to attempt to measure

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Abridgment of thesis submitted to the University of Minnesota in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Surgery (Minor Anatomy), March 20, 1930.



accurately the lacuna vasorum. Practically no reports have been made on the size of any of its contents, the femoral vein and artery or of its anterior boundary or Poupart's ligament. In this study all of these structures were considered in relation to crown-heel length, age, sex and side concerned.

#### THEORIES CONCERNING THE ETIOLOGY OF FEMORAL HERNIA

*Mechanical Theory.*—An old theory, known as the mechanical, in which abnormal length of the attaching membranes of the intestines was believed to be the main etiologic factor plus weakness of the

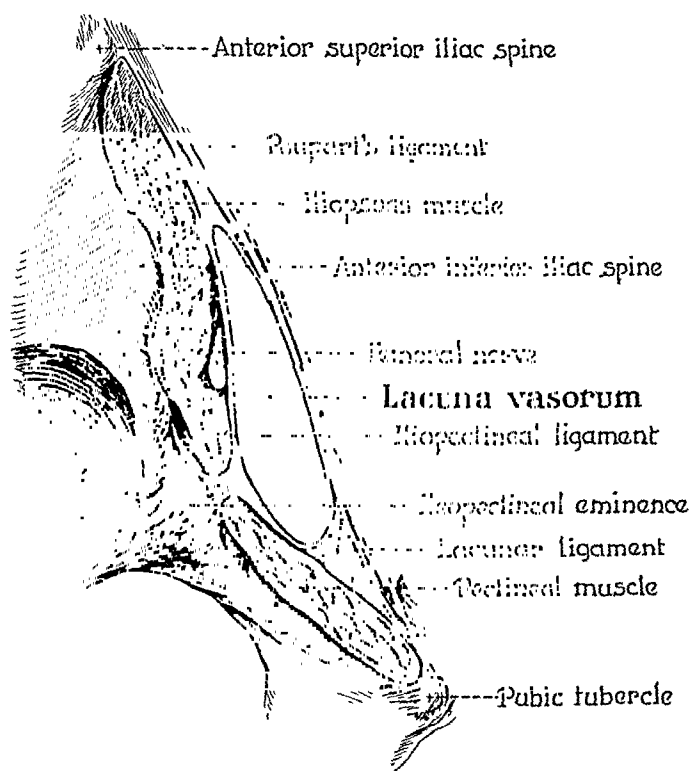


Fig. 1.—The lacuna vasorum.

abdominal parietes has few, if any, champions at present. Measurements made by Callender, Lockwood and Robinson showed that practically all mesenteries were long enough to reach well below the inguinal and femoral rings, and that persons with hernia failed to show any abnormality in the length of their mesenteries.

*Pressure Theory.*—Sir Arthur Keith (1906) said: "Most of us believe that two conditions are necessary for the production of a hernia: (1) a single or repeated sudden rise in intra-abdominal pressure; (2) a weak spot in the abdominal wall." He believed that the subperitoneal tissue in the femoral region was lax, and that the movable peritoneum was forced into a defect, the femoral ring, by one or more repeated

forces arising intra-abdominally. He also stressed the effect of exercise, coughing and straining on the expansion of the femoral vein above its valves acting as a water hammer and thereby increasing the size of the defect already present, thus allowing the protrusion of a diverticulum of peritoneum.

Hare agreed with Keith and believed that the upright position assumed by man increases the intra-abdominal pressure, as do heavy occupations, coughing, dyspnea, etc., while age and obesity, paralysis and emaciation weaken the supporting walls.

Along the same line, Battle stated: "The original cause of the hernia (femoral hernia) is not the formation of a peritoneal pouch, that is secondary to other things." Pilcher believed that in the aged there is a gradual relaxation of the structures forming the femoral canal. He felt, however, that femoral hernias are of congenital origin in children. Harvey stated that femoral hernias are never of congenital origin. Haynes concluded that the presence of a large easily compressible vein near a distinctly weak spot in the abdominal wall is an important factor, especially as the vein leaves the cavity in a straight line and not obliquely as does the spermatic cord through the inguinal canal. He thought that the only reason there were so few femoral hernias is that this weak area fortunately is small in extent in most cases.

Denny considered pregnancy a predisposing cause, since he considered that the fascia was weakened and the opening enlarged as a result of the strain accompanying labor. He further stated that the intestine itself passes through a patulous ring forming its own canal by pressing forward those parts in front of it that have the least resistance.

*Traction Theory.*—(a) Congenital or Preformed Sac Theory: Since 1902, Russell of Australia has been the chief defender of the saccular theory in regard to the causation of femoral hernia. Much the same idea was put forth by Jaboulay as early as 1899, and Dussac in 1900. Russell believed that the sac is formed prior to the development of the hernia, but that it need not be present at birth. According to him, during the second month of fetal life at the time the limb-buds and pleuroperitoneal cavity are forming, the blood vessels are also being developed, including those to the future limbs. It is possible, he believed, that at this time a small pouch of peritoneum from the embryonal pleuroperitoneal cavity may be involved in this growth process and attach itself to the femoral artery. Later, as the blood vessels develop and push down the extremity, this pouch of peritoneum is also pulled down with them through the ring. The sac is never discovered at birth,

because the diverticulum is too small at this time, but later as the limb grows the blood vessels lengthen and carry along this attachment of peritoneum. This theory is the only one, he felt, that could explain why a femoral hernia sac after leaving the saphenous opening takes its usual upward course. Russell's idea is that this is accomplished by the pull of one or more of the branches of the femoral artery. The loculated sacs described by Macready and Middleton are used to substantiate this theory further. Each locus is thought to follow one of the three main branches of the femoral artery: the superficial circumflex iliac artery, the superficial epigastric artery and the superficial external pudendal. The type of femoral hernia that goes down the thigh follows the main femoral vessels.

Russell carried this theory into practical use surgically, and does not believe that it is necessary to do more than remove the femoral sac and leave the ring entirely unaltered. Keith believed, however, that Russell effectually plugged the canal by leaving a wad of peritoneum after twisting and ligating the sac.

Middleton, LaRoque, Coley, Watson, Erdmann, Horsley, Lang and Pantan concur with Russell's ideas.

The arguments against the foregoing theory are many. At no stage in the development of the fetus up to the time of birth has any one demonstrated such a diverticulum. Sir Arthur Keith (1928) dissected over 500 bodies without ever seeing one. Dr. Scammon (1930) similarly examined 300 and never noted this condition. In over 100 bodies that I dissected with this point in view, there was no suggestion of its occurrence in a single instance. The case of a femoral hernia in a 3 months old fetus reported by Cushier in 1892 can hardly be considered as approaching in any way the character of the ordinary femoral hernia. In her case the integument had been broken through, and the intestines were lying out on the thigh. There were also other gross defects present. She reported that Picquet in 1846 had a case almost similar. In his case the liver and the intestine protruded through the ring although the skin was still intact.

Studies on the growth of blood vessels seem to indicate that they do not grow with the limb by extending outward, but that lineal growth of blood vessels is closely correlated with the lineal growth of adjacent tissues (Scammon, Schwalbe). Vessels do not recede further from the trunk with growth; if they did, the recurrent vessels so numerous in the four extremities would be pulled away from their destinations instead of toward them.

The change of the course upward of femoral hernia is explained by Haynes by two factors: (1) the cribriform fascia is more firmly attached at its lower than at its upper margin; (2) the superficial veins,

the pubic, the epigastric and the circumflex iliac, empty into the saphenous vein before it enters the femoral vein, and consequently these vessels would have to be stretched or displaced in order to allow the hernia to go downward.

As to the loculated sacs, the femoral region is by no means the only place they occur. Bevan described them in the inguinal region. McQueeney found 9 cases of multiple sacs in 129 hernias of various types. In 1900, Moynihan reported a large number of properitoneal and interstitial hernia, which were all bilocular. It would be difficult to attribute any of these to the effect of growth of blood vessels.

(b) Theory of Gubernacular Pull: Murray also believed that the femoral hernial sac is preformed but thought that the gubernaculum is responsible for its presence. Although there is no proof that the gubernaculum is in any way responsible for the descent of the testicle into the scrotum or for the formation of the processus vaginalis, he used this as the basis of his ideas. He believed that abnormal bands of this tissue often end elsewhere than in the scrotum, and that usually these abnormal bands are slender. Occasionally, however, a larger abnormal crural band is formed which, because of its function of pulling on the peritoneum, produces a diverticulum in the region of the crural ring, and with the growth of the individual a larger and true hernial sac is formed. He thought that this is the explanation for Ferguson's and Fauntleroy's cases of cruroscrotal hernia. To substantiate this hypothesis, he had the fundus of a femoral hernial sac examined microscopically and found striated muscle fibers present. Piersol described the gubernaculum testis to be made up of smooth muscle fibers and connective tissue, except its lowest portion which is made up of striated muscle derived from the muscles of the abdominal wall. After birth the gubernaculum becomes almost entirely atrophic and gives little if any evidence of muscle content. If this was the cause of femoral hernia, it seems strange that women show such a preponderance of femoral hernia over men, even though similar but much smaller and more slender bands are present in the former.

(c) Theory of Traction by Fat: Paré probably was the first to describe fatty hernia and to regard fat as a likely cause of intestinal hernia. Littré also described fatty hernia, or hernia adiposa. Since then many similar cases have been described. These hernias arise in the properitoneal fat and find their way through the femoral canal and out through the saphenous opening. Many are made up entirely of fat; many others have in their centers small diverticula of peritoneum. Even the largest of femoral hernial sacs has, as a general rule, a thick covering of fat surrounding them, especially at the fundus. Annandale, in 1869,

quoted Quain, who believed that the protrusion of the fatty mass was the first condition present in the formation of a hernia, a process or tube of peritoneum being gradually drawn down into it secondarily. Haas, in 1896, stated that he believed that the fat found at the lowest part of the sac was the causative factor in the development of this form of hernia, and that the fat first dilated the ring and then dragged along a pouch of peritoneum with it. The fat was probably forced along by muscular action and not, he thought, by reason of its weight alone.

Buckley called this same process "the acquired saccular theory." According to him, there is a weakness of the abdominal wall, and in the case of the femoral hernia this is present at the crural ring. There is also an accumulation of loose properitoneal fat with adhesions from it to the peritoneum and also to the fat that plugs the crural canal. The peritoneum is loose and can be easily stretched. Increased intra-

TABLE 1.—*Frequency of the More Common Types of Hernia*

Author	Year	Total Number of Hernia	Inguinal	Femoral	Others
Parker.....	1893	190	137	25	28
Stinson.....	1896	97	79	5	13
Pott.....	1903	15,028	14,095	933	..
Morison.....	1904	95	75	10	10
Hilgenreiner.....	1904	891	651	119	21
De Garmo.....	1905	1,250	1,140	110	..
Bull and Coley.....	1905	53,686	50,961	2,725	..
Pfister.....	1906	300	234	35	31
Stephens.....	1926	2,090 (men)	2,051	39	..
McQueeney.....	1926	129	95	8	26
		73,756	70,115	4,009	129

abdominal pressure forces the fat into the canal and then out under Poupart's ligament and with it the properitoneal fat. The latter, then, in many cases carries with it a diverticulum of peritoneal. This process is probably a very slow one. After a pouch is formed it may later become further distended because of the presence of abdominal contents within it. Pressure atrophy tends to thin out the fat surrounding large femoral hernial sacs.

Keith (1906) believed it is possible for the fat, because of its semi-fluid nature, to act as a water hammer and force its way under Poupart's ligament carrying with it the peritoneum, and that this same process accounts for the herniation of properitoneal fat seen in the linea alba. Here also the vessels pass through vascular foramina.

Lutz, Keyes, Souttar, Friedman, Parker, McQueeney and Roeder favor this explanation.

#### CLINICAL STUDY

*Incidence.*—From 1909 to 1928, inclusive, there were seen at the University Hospital 52 patients with femoral hernia. Forty-five of these

were treated surgically and 7 were not. In the latter group a few refused operation, and in others some disability was present which contraindicated surgical treatment. During this same period there were 1,130 patients with inguinal hernia, or a proportion of 21 inguinal to 1 femoral.

Table 1 shows the figures given by various authors as to the frequency of the various types of the more common hernia. From these figures, the proportion of inguinal hernia to femoral is found to be 17:1.

*Sex Distribution.*—There were 16 males and 36 females in this series, or a proportion of 1 male to 2.2 females.

Table 2 shows the figures as to sex distribution collected from other authors. The proportion of males to females is 1:2.3. Coley, in 1906, found the proportion to be 1:6 in adults and 1:2 in children.

TABLE 2.—*Sex Distribution in Femoral Hernia*

Author	Year	Total Number of Cases	Males	Females
Bull and Coley.....	1898	1,927	558	1,369
Hilgenreiner.....	1904	119	13	106
De Garmo.....	1905	99	16	83
Pfister.....	1906	35	7	28
Battle.....	1908	81	14	67
Bachelor.....	1909	15	5	10
Groves.....	1923	22	1	21
Harvey.....	1924	52	28	24
Herzfeld.....	1924	4	1	3
Coley.....	1924	101	43	58
Rutherford.....	1927	5	1	4
Totals.....		2,460	687	1,773

Keith (1925) concluded from collected figures that out of every 1,000 ruptured males, 970 would have inguinal, 20 femoral and 10 umbilical hernia; while out of 1,000 ruptured females, 500 would have inguinal, 340 femoral and 160 umbilical hernia. Berger stated that 37.1 per cent of all hernia in females are femoral, while only 6.6 per cent are femoral in males.

*Age Incidence.*—The peak age incidence for this condition begins at the age of 25 and ends at 45 (fig. 2). During this period of twenty years occur 44 per cent of all cases. Berger found the peak in females to begin at 45 and end at 80, with the maximum point at 70 years of age. De Garmo (1905) found the peak somewhat earlier in life, from 20 to 50 years.

Femoral hernias are rare in children. Sabourin reported a case in a premature infant. The youngest patient in our series was 6 years of age. There was one other child under 10. Bull and Coley reported 69 of 2,179 cases of femoral hernia to be in children under 14, but only 13 of those were under 10 years of age. The youngest patient in their series was 2 years old. Wernher reported 7 children under 5.

Hilgenreiner reported 3 of 119 patients to be under 20; Harvey, 1 child in 52 cases, and Stiles only 1 in 360 cases. MacLennan found only 6 femoral hernias in children to 1,000 inguinal. Murray, in 1910, collected the records of 104 cases of femoral hernia in children under 15 years of age.

Macready gives the following statistics as to the age incidence for children under 20: Of 134 males, there were 7 from 1 to 5 years of age, 19 from 6 to 10, 29 from 11 to 15 and 29 from 16 to 20; of 338 females, there were 8 from 1 to 5, 22 from 6 to 10, 50 from 11 to 15 and 258 from 16 to 20 years of age.

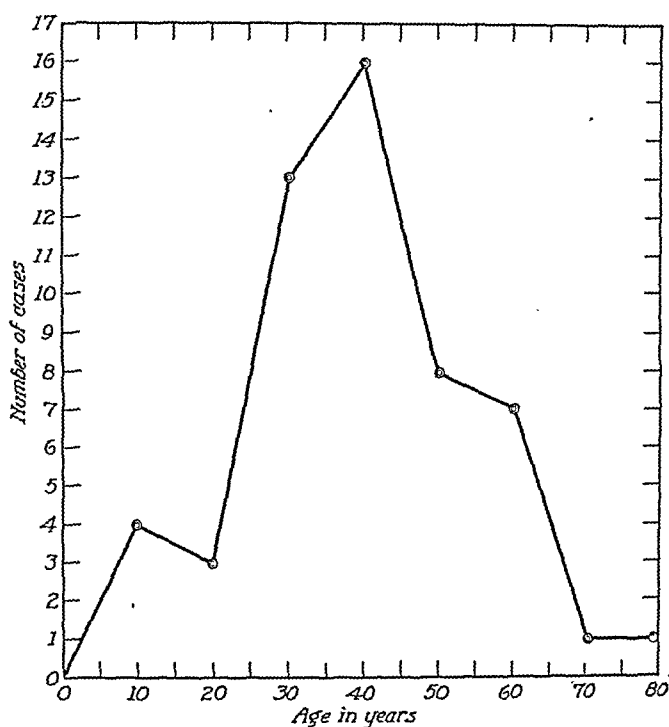


Fig. 2.—The incidence of femoral hernia according to age.

*Distribution of Femoral Hernia as to Side.*—In our series of cases, 33 hernias developed on the right side, 18 on the left and in 2 cases they were bilateral. Sixty-three per cent were right-sided.

Table 3 shows that 60 per cent of femoral hernias are on the right side.

Bigg found that in 100 femoral hernias in women 52 were on the right side, 40 on the left and 8 were bilateral; while in men, 50 were on the right side, 33 on the left and 17 were bilateral.

Piersol stated:

The almost invariable preponderance of right-sided hernia in all varieties, at all ages, in both sexes has been variously attributed to (a) the greater bulk and

weight of the liver; (b) to right-sidedness in walking and lying, and to the greater strain on the muscles of the right side caused by "right-handedness"; (c) to the inclination from left to right of the mesentery of the small intestine as it descends; (d) to the greater frequency of incomplete descent of the testes and of a patulous funicular process on the right side; and (e) to the larger capacity and circumference of the right side of the pelvis (Knox, Macready) as compared with the left, causing a corresponding increase in the size of the right femoral ring.

*The Effect of Pregnancy on the Occurrence of Femoral Hernia.*—There were 36 females in the series from the University Hospital. In two of these no mention was made of whether or not the patient had children. Eight females (which includes 3 children) had had no pregnancies. Four women had only a child each, while 24 had more, with an average number of 6.4 children for each woman.

Kingdon found that in 138 single women who were ruptured 68 had inguinal and 70 femoral hernia; in 32 married but childless women

TABLE 3.—*Distribution of Femoral Hernia as to Side*

Author	Year	Total Number of Cases	Right	Left	Bilateral
De Garmo.....	1905	99	59	29	11
Battle.....	1908	81	43	38	..
Harvey.....	1924	52	37	15	..
Totals.....		232	139	82	11

15 had inguinal and 17 femoral hernia, while in 511 mothers 313 had femoral and only 198 inguinal hernia.

Birkett found that in 193 ruptured females under 15 years of age 184 had inguinal hernia and 9 femoral; in 111 single women 50 had inguinal hernia and 62 femoral, while in 440 mothers 178 had inguinal and 262 femoral hernia.

Macready found that the number of single women as compared to the married and widowed between the ages of 20 and 45 was 1:1.5, and that the ratio of women who have borne children to those who have not was 1.2:1. In ruptured females the childless are to the mothers as 1:2.7.

*Contents of the Femoral Sac.*—In 20 cases in the University Hospital series the contents of the sac were not recorded. In 7 instances no operation was performed. In the remaining cases, 12 sacs were entirely empty, 6 contained normal omentum, 6 strangulated omentum and 4 strangulated bowel. In no case was normal bowel found. About 20 per cent of the patients, then, were operated on primarily because of strangulation. Morton operated on 27 of 47 patients for this reason and Bachelor on 52 of 182.



Murphy reported Fantino's findings in 4,200 cases of hernia, in which 6.54 per cent of the inguinal hernias and 38 per cent of the femoral were strangulated.

Table 4 shows that more than 40 per cent of all strangulated hernia are femoral, while only 5 per cent of all hernia belong to this type. Femoral hernias, then, are eight times more liable to become strangulated than inguinal.

*Recurrences Following Operation for Femoral Hernia.*—Of the 52 patients admitted to the University Hospital with femoral hernia, 6 gave a history of having had a previous operation for the same condition.

Keynes stated that at the City of London Truss Society, over a ten year period, 350 patients were seen with recurrences and that of these

TABLE 4.—*Strangulated Hernia*

Author	Year	Total Number of Cases	Inguinal	Femoral	Others
Parker.....	1893	61	30	21	10
Thorburn.....	1903	110	55	37	18
Hilgenreiner.....	1904	362	208	134	20
Erdmann.....	1904	58	31	19	8
Hilton.....	1907	529	250	250	29
Alexander.....	1913	105	60	25	20
Totals.....		1,225	634	466	105

TABLE 5.—*Recurrences Following Operations for Femoral Hernia*

Author	Year	Total Number of Cases	Recurrences
De Garmo.....	1905	99	3 (not all traced)
Bachelor.....	1909	103	1
Coley and Hoguet.....	1918	99	14
Groves.....	1923	21	0
Coley.....	1924	28	3
Harvey.....	1924	46	0
Stephens.....	1926	39	4

275 were inguinal and 90 femoral hernias. As 17 inguinal hernias are found to 1 femoral, one may conclude that femoral hernias are several times (4:5) more liable to recurrence than inguinal.

In order to determine, if possible, the number of recurrences following the operations for femoral hernia performed at the University Hospital, questionnaires were sent to each of these patients.

Out of the 45 letters sent out, 20 were returned unopened.<sup>1</sup> Of the 25 people who answered, 23 were entirely free from recurrence while in 2 there was definite evidence of a return of their former trouble. Both of these patients were unable to come back to the hospital for an examination.

1. The transient residence of the class of patient admitted to the University of Minnesota Hospital makes an adequate follow-up very unsatisfactory.

Statistics on the number of recurrences following operation for femoral hernia are relatively few.

Watson collected the figures from various clinics and in 1,444 cases found recurrence present in less than 5 per cent.

In 182 in which a muscle plastic operation was done, there were 9.89 per cent recurrences.

Noble said that a fair estimate for recurrence in inguinal hernia is from 3 to 5 per cent, while for femoral hernia it is from 25 to 30 per cent.

For many years there has existed a controversy as to whether or not it is necessary for the femoral canal to be closed after the sac is removed to obtain a cure. Pott found that in those cases in which the sac only was removed for the repair of femoral hernia, there were 63.3 per cent cures, while in those cases in which the sac was ligated and the ring closed, the cures were 76.4 per cent. Bull, in 1890, treated 13 patients by simple ligation of the sac, and one year later he was able to trace 8 with 3 recurrences. Bresset studied 395 femoral hernias, and in 232 cases without closure of the ring found 29 per cent recurrence, while in 163 with closure of the ring recurrence took place in only 8.6 per cent. Keynes, quoting the work of Professor Gask, stated that the latter in order to test the point as to whether or not it was necessary to close the ring to obtain a cure in femoral hernia merely removed the sac in 10 cases through a laparotomy incision. He found 6 prompt recurrences. However, Russell, LaRoque, the late Ochsner and others claim excellent results by simply removing the sac from below.

#### ANATOMIC STUDIES

Very few measurements have been made of the structures concerned in the formation of femoral hernia. Books on anatomy and surgery with few exceptions and without any apparent proof state that femoral hernia are found more often in females than in males because the femoral ring is larger in the former. To measure accurately the femoral ring is impossible because of its variable lateral wall, the femoral vein. The best indirect method to secure this information was to measure the lacuna vasorum and the vessels, then by subtracting the sum of the diameters of the vessels from the cross-section area of the lacuna one could determine the approximate size of the ring, or the amount of space available for the development of a femoral hernia. Panton, in 1922, first showed that the distance from the anterior superior spine of the ilium to the pubic spine (Poupart's ligament) was smaller in females than males. He also made linear measurements of the lacuna vasorum and concluded that this structure was larger in females than in males.

In this study the lacuna vasorum was measured by accurately cutting and fitting into its ligamentous borders a piece of celluloid and then determining the surface area of this form by means of a planimeter. The length of Poupart's ligament was taken to be the distance from the anterior superior iliac spine to the pubic tubercle measured with pointed calipers. The caliber of the vessels was determined by using accurately calibrated cones (fig. 3). The thickness of the vessel walls was obtained by the use of an ordinary beam-caliper with a vernier attachment allowing readings to be made to 0.1 mm.

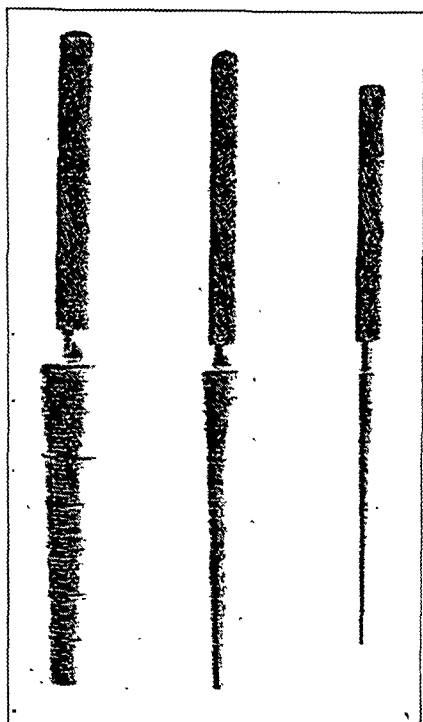


Fig. 3.—Calibrated cones used in the measurement of the diameter of the femoral vessels.

Fresh autopsy specimens only were used. Grossly pathologic pelvises were eliminated; otherwise the material was unselected.

Thirty female and 34 male premature and new-born infants, 8 children of various ages, 30 women and 30 men were examined and measured. Height and age were correctly recorded. All hernial sacs in the femoral and inguinal regions were noted.

#### TREATMENT OF DATA

In order to ascertain more fully the significance of the data collected, it was necessary to apply to it both graphical and numerical analytic methods. The data was first arranged into five tables (tables 6, 7, 8, 9 and 10).

TABLE 6.—Measurements of the Lacuna Vasorum and Associated Structures in Thirty-Four Male Premature and New-Born Infants

	Right Side					Left Side				Processus Vaginalis			
C-H Length, Cm.	Lacuna Vasorum, Sq. Mm.	Poupart's Ligament, Cm.	Caliber of Vein, Mm.	Caliber of Artery, Mm.	Lacuna Vasorum, Sq. Mm.	Poupart's Ligament, Cm.	Caliber of Vein, Mm.	Caliber of Artery, Mm.	Both Open	Right Open	Left Open	Both Closed	
34	18	2.3	1.7	1.0	17	2.3	1.6	1.0	+	+	—	—	
36	22	2.3	1.7	1.0	25	2.3	1.7	1.0	+	—	—	—	
37	28	2.3	1.8	1.0	32	2.3	1.7	1.0	+	—	—	—	
38	37	3.1	...	...	34	3.1	...	...	+	—	—	—	
39	28	2.8	1.6	1.1	32	2.9	1.7	1.2	—	+	—	—	
39	30	3.1	2.9	1.0	32	3.1	3.2	1.1	+	—	—	—	
40	55	2.8	1.7	1.1	43	2.6	1.9	1.3	+	—	—	—	
40	26	2.9	1.9	1.0	24	2.9	2.1	1.1	+	—	—	—	
40	31	3.0	2.2	1.2	28	3.0	2.3	1.2	+	—	—	—	
41	26	3.2	1.7	1.0	31	3.2	1.6	1.0	+	—	—	—	
41	28	2.7	2.1	1.1	30	2.7	2.2	1.0	+	+	—	—	
41	28	2.8	1.6	1.0	27	2.8	1.7	1.0	—	—	—	—	
42	28	2.9	1.6	1.1	35	2.8	1.7	1.1	+	—	—	—	
42	31	3.7	1.2	1.1	30	3.7	1.7	1.1	+	—	—	—	
43	35	3.6	2.7	1.0	33	3.6	2.8	1.0	+	—	—	—	
44	46	3.3	2.0	1.2	47	3.4	1.9	1.3	+	—	—	—	
45	62	3.6	2.4	1.1	54	3.5	2.5	1.1	—	+	—	—	
46	40	3.5	2.4	1.2	42	3.4	2.7	1.2	+	—	—	—	
46	35	3.0	3.8	1.5	34	3.0	3.4	1.4	—	—	—	+	
48	50	3.6	1.8	1.1	39	3.6	2.0	1.1	+	—	—	—	
48	52	3.7	2.7	1.2	46	3.7	2.8	1.2	—	—	—	+	
49	40	3.7	1.8	1.4	50	3.8	1.7	1.3	—	—	—	+	
50	40	3.3	2.1	1.2	50	3.4	2.0	1.2	—	+	—	—	
50	36	4.2	2.2	1.2	35	4.1	2.2	1.2	+	—	—	—	
52	66	4.1	2.4	1.4	56	4.2	2.9	1.6	—	—	—	+	
52	55	4.0	2.6	1.9	50	3.9	2.9	1.9	—	—	—	+	
52	44	3.2	2.0	1.1	45	3.1	1.9	1.1	—	+	—	—	
52	41	4.6	2.8	1.2	38	4.6	2.9	1.2	—	+	—	—	
52	40	3.6	2.6	1.1	41	3.5	2.2	1.1	—	—	—	+	
52	64	4.0	3.0	1.5	57	4.1	4.8	1.4	+	—	—	—	
52	46	4.0	3.0	1.4	39	3.9	3.2	1.5	—	—	—	+	
53	61	3.8	2.8	1.1	62	3.8	2.6	1.1	—	+	—	—	
53	46	4.0	1.6	1.3	60	3.9	2.8	1.3	—	—	+	—	
53	67	4.1	3.7	1.7	57	4.2	3.9	1.7	—	—	—	+	
Average—	40.6	3.38	2.31	1.18	39.6	3.37	2.39	1.20	Total—	18	7	1	
45.3												8	

TABLE 7.—Measurements of the Lacuna Vasorum and Associated Structures in Thirty Female Premature and New-Born Infants

	Right Side				Left Side				Processus Vaginalis					
	C-H Length, Cm.	Lacuna Vasorum, Sq. Mm.	Poupart's Ligament, Cm.	Caliber of Vein, Mm.	Caliber of Artery, Mm.	Lacuna Vasorum, Sq. Mm.	Poupart's Ligament, Cm.	Caliber of Vein, Mm.	Caliber of Artery, Mm.	Both Open	Right Open	Left Open	Both Closed	
35	32	2.3	1.6	1.0	31	2.3	1.6	1.0	1.0	+	—	—	—	
37	23	2.7	1.4	1.0	22	2.6	1.3	1.0	1.0	—	—	—	+	
38	27	2.4	1.5	1.1	30	2.4	1.6	1.1	1.1	—	—	—	+	
38	22	2.6	1.8	1.0	23	2.8	1.8	1.0	1.0	—	—	—	+	
38	23	3.3	2.8	1.2	24	3.3	2.8	1.2	1.2	—	—	—	+	
39	35	2.8	1.7	1.1	32	2.6	1.9	1.3	1.3	—	—	—	+	
39	23	2.9	1.6	1.0	26	2.9	1.5	1.0	1.0	+	—	—	—	
39	29	2.9	2.3	1.0	23	2.9	2.2	1.0	1.0	—	+	—	—	
41	23	3.0	1.7	1.0	36	2.9	1.8	1.0	1.0	—	—	—	+	
42	32	2.8	2.6	1.4	30	2.8	2.8	1.0	1.0	—	—	—	+	
43	32	3.1	2.2	1.1	26	3.1	1.9	1.1	1.1	—	—	—	+	
43	39	3.0	1.6	1.0	38	2.9	2.7	1.1	1.1	—	—	—	+	
43	27	3.0	2.4	1.2	30	2.8	2.4	1.4	1.4	—	—	—	+	
44	50	2.8	...	...	35	2.9	...	...	...	—	—	—	+	
44	42	3.3	2.2	1.4	44	3.3	...	...	...	—	—	—	+	
44	46	3.5	2.7	1.2	45	3.6	2.6	1.2	1.2	—	+	—	+	
46	30	3.0	1.4	1.4	29	3.1	2.3	1.3	1.3	—	—	—	+	
46	45	3.7	2.0	1.1	41	3.7	1.9	1.2	1.2	—	—	—	+	
48	36	3.6	1.8	1.1	43	3.5	1.6	1.1	1.1	—	—	—	+	
48	40	3.7	2.3	1.3	32	3.7	2.4	1.3	1.3	—	—	—	+	
48	32	3.5	2.3	1.3	35	3.5	2.6	1.2	1.2	—	—	—	+	
49	50	3.5	1.6	1.3	36	3.6	1.9	1.3	1.3	—	—	—	+	
49	48	3.5	1.2	1.2	29	3.3	2.7	1.1	1.1	—	—	—	+	
52	47	3.9	1.2	1.2	39	3.9	2.4	1.4	1.4	—	—	—	+	
52	38	3.3	1.1	1.1	40	3.5	1.8	1.1	1.1	—	—	—	+	
52	41	3.3	1.1	1.1	42	3.3	2.2	1.2	1.2	—	—	—	+	
53	60	4.2	1.7	1.7	46	3.9	2.4	1.9	1.9	—	+	—	+	
53	52	4.0	1.8	1.3	46	4.0	2.7	1.6	1.6	—	—	—	+	
54	51	4.1	1.3	1.3	58	4.1	2.7	1.3	1.3	—	—	—	+	
54	59	3.9	1.2	1.2	68	3.9	2.7	1.3	1.3	—	—	—	+	
Average—	45.1	38.6	3.25	2.15	1.20	38.1	3.23	2.22	1.22	Total—	2	3	0	25

TABLE 8.—Measurements of the *Lacuna Vasorum* and Associated Structures in Thirty Men

Age, Years	Length, Cm.	Estimated Weight, Pounds	Right Side								Left Side								Hernial Sacs	
			Lacuna Vasorum, Sq. Mm.	Poupart's Ligament, Cm.	Vein		Artery		Lacuna Vasorum, Sq. Mm.	Poupart's Ligament, Cm.	Vein		Artery		Lacuna Vasorum, Sq. Mm.	Poupart's Ligament, Cm.	Caliber, Mm.	Wall, Mm.	Inginal	Femoral
					Caliber, Mm.	Wall, Mm.	Caliber, Mm.	Wall, Mm.			Caliber, Mm.	Wall, Mm.	Caliber, Mm.	Wall, Mm.						
19	166	120	300	13.6	10.8	0.5	5.4	0.9	240	13.6	10.8	0.6	8.2	1.0						
37	169	110	390	12.3	9.8	0.4	6.1	1.0	270	12.2	9.4	0.4	5.8	1.1						
39	177	170	310	14.6	12.0	0.5	5.8	1.3	280	14.6	12.4	0.3	3.8	1.2						
39	175	170	320	12.7	9.2	0.6	5.3	1.1	300	12.8	9.4	0.6	5.1	1.0						
44	172	160	430	13.1	9.6	0.7	4.8	1.4	420	13.1	10.1	0.6	4.9	1.5						
45	173	120	640	12.4	8.5	0.7	4.2	1.3	550	12.2	8.4	1.0	4.1	1.2						
45	181	135	510	13.9	8.9	0.6	5.6	1.1	490	13.9	8.7	0.5	5.7	1.0						
53	168	140	390	13.4	9.8	1.0	7.0	1.2	430	13.4	9.6	1.0	7.2	1.2						
54	177	159	390	11.5	12.6	0.5	5.4	1.0	350	11.4	11.2	0.4	5.4	1.5					Right	
55	176	160	360	11.3	9.1	0.6	7.8	1.1	310	11.1	9.2	0.6	8.4	1.2						
57	165	120	420	12.6	11.2	0.5	6.8	1.2	430	12.2	10.8	0.5	7.0	1.1						
59	189	140	490	17.0	10.1	0.6	8.4	1.0	400	17.1	9.4	0.6	8.3	1.2						
59	174	189	590	12.8	14.2	0.6	9.6	1.1	580	12.9	12.0	0.6	9.4	1.2						
59	165	140	320	11.9	11.8	0.7	7.0	1.6	280	11.8	12.0	0.7	7.2	1.5						
59	168	140	420	12.3	9.6	0.7	8.2	1.2	460	12.3	9.4	0.6	7.0	1.3					Right	
60	173	160	530	13.3	10.2	0.8	7.0	1.3	510	13.3	9.8	0.8	6.3	1.4					Right	
60	177	160	590	12.8	9.0	0.5	5.2	1.2	550	12.5	9.2	0.5	5.4	1.2						
61	161	160	520	12.3	12.0	0.6	5.2	1.2	340	12.6	10.4	0.6	5.4	1.4					Left	
62	175	160	660	14.5	11.8	1.7	7.2	1.1	780	14.3	11.2	0.7	7.7	1.3					Right	
62	170	160	420	11.3	8.2	0.6	6.4	1.6	350	11.3	7.8	0.6	5.7	1.7						
65	171	180	360	12.6	12.0	0.6	8.9	0.9	400	12.5	11.2	0.5	9.4	1.1					Right	
68	174	160	250	11.6	12.0	0.6	8.3	1.3	300	12.0	16.0	0.7	8.7	1.3						
69	170	165	640	14.4	11.8	0.7	7.7	1.1	700	13.9	11.0	0.6	7.6	1.0					Bilateral	
69	175	160	540	12.3	8.0	0.8	6.4	1.6	500	12.2	8.3	0.7	5.2	1.2						
69	167	170	370	12.8	11.2	0.6	5.2	1.3	340	12.6	10.4	0.6	5.4	1.4					Left	
70	178	190	400	13.0	10.0	0.5	8.0	1.1	410	13.1	10.2	0.5	7.4	1.0						
71	175	200	450	15.4	10.0	0.6	8.0	1.8	380	15.4	9.4	0.6	8.4	1.8					Bilateral	
71	186	150	500	12.4	9.8	0.7	5.7	1.3	390	12.4	9.0	0.8	7.7	1.4						
77	167	150	640	13.1	10.2	0.6	9.7	1.0	650	13.1	10.2	0.7	8.6	1.1						
79	173	145	400	13.7	9.6	0.7	7.0	1.4	410	13.8	9.8	0.7	7.5	1.3						
Average—																			Total—	
58	173		451	13.03	10.43	0.68	6.77	1.22	430.6	12.97	10.25	0.63	6.8	1.26					8	3

TABLE 9.—Measurements of the *Lacuna Vasorum* and Associated Structures in Thirty Women

Age, Years	Length, Cm.	Estimated Weight, Pounds	Right Side								Left Side								Hernial Sacs	
			Lacuna Vasorum, Sq. Mm.	Poupart's Ligament, Cm.	Vein		Artery		Lacuna Vasorum, Sq. Mm.	Poupart's Ligament, Cm.	Vein		Artery		No. Children	Inguinal	Femoral			
					Caliber, Mm.	Wall, Mm.	Caliber, Mm.	Wall, Mm.			Caliber, Mm.	Wall, Mm.	Caliber, Mm.	Wall, Mm.						
18	150	110	280	10.9	9.0	0.4	5.8	1.1	350	10.9	9.2	0.4	5.2	1.1	0	—	—			
21	163	130	260	12.2	8.0	0.4	6.8	1.0	250	12.0	9.0	0.4	7.0	1.0	0	—	—			
22	155	125	280	11.4	8.0	0.6	3.7	1.0	320	11.5	7.4	0.6	3.4	1.0	1	—	—			
27	165	135	230	11.2	9.8	0.5	4.7	0.8	270	11.2	11.2	0.5	5.0	0.9	0	—	—			
28	159	110	230	12.4	9.0	0.3	5.0	1.0	260	12.2	9.4	0.4	4.8	0.9	1	—	—			
28	168	120	260	13.3	10.4	0.4	6.2	1.0	290	13.3	10.2	0.4	5.8	1.0	5	—	—			
35	159	135	300	12.3	11.0	0.9	5.6	1.4	380	12.3	10.8	0.8	5.8	1.4	0	—	—			
38	166	110	470	11.8	9.2	0.6	4.8	1.0	350	11.6	8.3	0.5	4.4	1.2	0	—	Right			
39	154	110	250	13.4	8.4	0.5	4.8	0.9	290	13.6	8.0	0.4	5.2	0.9	0	—	Right			
39	158	100	320	12.8	11.0	0.4	5.8	1.0	300	12.8	9.8	0.4	5.3	0.9	9	—	—			
40	155	130	280	12.9	8.4	0.7	5.4	1.2	250	13.1	8.2	0.6	5.1	1.1	7	—	—			
41	152	100	420	13.1	6.2	0.5	3.1	1.0	370	13.1	6.6	0.5	3.1	1.0	1	—	—			
42	158	150	300	11.6	10.2	0.5	4.8	0.9	340	11.7	9.8	0.6	5.0	0.9	6	—	—			
44	157	110	250	13.2	11.4	0.6	5.4	1.0	360	13.2	11.4	0.7	5.8	1.2	0	—	—			
44	167	120	320	12.8	5.4	0.6	4.6	1.0	370	12.7	5.6	0.6	4.4	1.0	4	—	—			
45	162	140	370	14.0	7.8	0.7	3.8	1.2	400	13.9	8.2	0.7	4.1	1.2	3	—	—			
48	164	145	410	12.8	9.6	0.6	5.6	1.2	480	12.8	9.0	0.7	6.0	1.3	8	—	—			
55	162	110	380	13.1	12.0	0.5	6.3	1.1	400	13.0	16.0	0.5	6.2	1.2	2	—	—			
55	154	175	300	11.4	10.4	0.5	6.8	1.1	300	11.4	9.6	0.4	6.4	1.0	1	—	Left			
55	167	130	410	14.3	9.3	0.6	7.5	1.2	490	14.4	9.5	0.7	7.2	1.2	7	—	—			
56	160	110	330	12.0	7.0	0.7	5.4	1.3	330	12.3	7.2	0.7	5.8	1.4	0	—	—			
56	158	110	230	12.8	9.8	0.7	7.6	1.0	220	13.0	9.5	0.7	7.2	1.0	0	—	—			
61	160	136	530	12.2	8.3	0.8	5.2	1.2	480	12.1	8.0	0.7	4.8	1.3	8	Right	—			
62	165	180	330	12.7	11.4	0.6	9.2	1.2	430	12.8	11.0	0.6	9.3	1.1	11	—	—			
62	168	180	510	12.8	10.0	0.5	4.2	1.2	350	12.9	9.2	0.5	4.8	1.3	9	—	—			
63	153	150	270	12.6	6.6	0.6	5.3	1.2	220	12.5	7.0	0.5	5.5	1.0	6	—	Bilat.			
66	158	145	400	11.4	10.4	0.6	6.0	0.9	330	11.6	10.4	0.7	5.8	1.0	12	—	—			
68	163	150	320	12.7	8.8	0.7	5.0	1.2	300	12.5	9.3	0.8	6.2	1.4	5	Left	Right			
73	155	160	1100	11.6	9.4	1.3	7.4	1.9	1050	11.2	9.1	0.9	7.4	1.8	3	Left	Right			
78	153	160	420	12.7	9.6	0.4	7.3	1.5	380	12.9	9.8	0.4	7.4	1.5	2	Total—	3			
Average—																				
47	160		360.6	12.5	9.19	0.58	5.04	1.12	363.7	12.5	9.26	0.58	5.63	1.14						

TABLE 10.—Measurements of the Lacuna Vasorum and Associated Structures in Eight Infants and Children—Both Sexes

Age	Sex	Length, Cm.	Estimated Weight, Pounds	Right Side								Left Side								Hernial Sacs	
				Lacuna Vasorum, Sq. Mm.	Poupart's Ligament, Cm.	Vein		Artery		Lacuna Vasorum, Sq. Mm.	Poupart's Ligament, Cm.	Vein		Artery		Inguinal	Femoral				
						Caliber, Mm.	Wall, Mm.	Caliber, Mm.	Wall, Mm.			Caliber, Mm.	Wall, Mm.	Caliber, Mm.	Wall, Mm.						
8 mo.	M	69	22	86	5.7	3.6	...	2.3	...	97	5.7	2.9	...	2.0	...	...	...				
8 yr.	M	120	60	210	8.6	5.3	0.3	2.8	0.5	150	8.4	4.8	0.3	2.9	0.5	...	...				
14 yr.	M	135	90	230	10.1	5.8	0.4	3.7	1.0	190	9.9	6.0	0.5	4.0	1.0	...	...				
6 mo.	F	58	10	65	5.1	2.4	...	1.7	...	71	5.0	2.6	...	2.0	...	...	...				
8 mo.	F	61	12	80	4.6	...	...	...	...	83	4.5	...	...	...	...	...	...				
14 yr.	F	155	100	290	11.4	8.2	0.5	4.4	0.8	240	11.4	8.4	0.5	4.1	0.8	...	...				
14 yr.	F	169	100	220	12.9	13.0	0.9	4.4	1.0	190	13.0	13.5	0.6	4.0	1.0	...	...				
16 yr.	F	160	95	280	13.5	7.8	0.4	4.2	0.8	260	13.5	7.0	0.4	4.2	0.8	...	...				

The procedure used in nearly every group can be divided into two classes: the numerical and graphical analytic methods. In the former were included the calculation of the numerical average of each set of figures, the determination of the coefficient of variability for each group of figures and the calculation of the Pearsonian coefficient of correlation.<sup>2</sup>

2. Pearson's formula for the coefficient of correlation is:

$$r = \frac{\Sigma (XY)}{N \delta_1 \delta_2}$$

where  $\Sigma (XY)$  equals the sum of the X deviations multiplied by the Y deviations, N is the number of cases,  $\delta_1$  is the standard deviation of X, and  $\delta_2$  is the standard deviation of Y.

The standard deviation is obtained by the following formula:

$$\sqrt{\frac{\Sigma d^2}{N}}$$

with  $d^2$  representing the sum of the deviations squared.

The probable error of the coefficient of correlation is obtained by the formula:

$$P.E. = \frac{0.67 (1 - r^2)}{\sqrt{N}}$$

where r represents the coefficient of correlation and N the number of cases.

The following conventions are often applied to the interpretation of the coefficient of correlation (King, W. I.: *The Elements of Statistical Method*, New York, The Macmillan Company, 1916, p. 215):

1. If r is less than the probable error, there is no evidence whatever of correlation.
2. If r is more than six times the size of the probable error, the existence of correlation is a practical certainty.
3. If r is less than 0.30, the correlation cannot be considered at all marked.
4. If r is above 0.50, there is decided correlation.

## SUMMARY OF OBSERVATIONS

*Premature and New-Born Infants.*—The average length for both sexes in the 34 male premature and new-born infants and the 30 females was very nearly equal—45.3 cm. for the males and 45.1 cm. for the females. In most cases the measurements of the male were quite appreciably larger than the female. The right side in nearly all cases was also slightly larger than the left, except in the case of the vessels.

The average area of the lacuna vasorum at birth (an average of all infants between the crown-heel length of 48 and 54 cm.) was 47 sq. mm. for the females and 49 sq. mm. for the males.

Among the 34 males the processus vaginalis was closed in 9, open bilaterally in 18, open on the right in 6 and on the left in 1. Among the 30 females it was closed in 25, open bilaterally in 2, open on the right side in 3 and on the left side in none.

*Adults.*—In adults the average length for the males was 172.9 cm. and for the females 159.6 cm. The difference in the size of the measurements corresponds fairly well with this inequality. The average age for the males was also higher—57.8 years and 46.9, respectively. The lacuna vasorum was found to be absolutely and also relatively larger in the male than in the female. In females the average crown-heel length was 159.6 cm. and the average lacunar area was 360 sq. mm. Then, with an average crown-heel length of 173 cm. for the males, the lacunar area of the latter should measure about 390 plus sq. mm., while it did measure 440 sq. mm., showing a definite increase over the female of about 50 sq. mm. The average measurements on the right side in most instances was greater than on the left, except in the case of the vessels.

In the 60 adults there were 6 femoral hernial sacs present, 3 in each of the sexes. In 5 the sacs were small, on the average from about  $\frac{3}{4}$  to 1 inch (1.9 to 2.5 cm.) in depth. In the sixth, which was present

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The coefficient of variability was obtained by the following formula:

$$\frac{\delta}{M} \times 100$$

where  $\delta$  is the standard deviation and M the arithmetic average. It is read in per cent.

The second type consists of field graphs in which the central tendency was established by means of a regression line. The points for the latter were obtained by the use of the following formula:

$$Y = r \frac{\delta Y}{\delta X} X - r \frac{\delta Y}{\delta X} \bar{X} + \bar{Y}$$

where Y is the ordinate, r the coefficient of correlation,  $\delta Y$  the standard deviation of Y,  $\delta X$  the standard deviation of X, X the abscissa,  $\bar{X}$  the mean of the abscissa and  $\bar{Y}$  the mean of the ordinate.

in a female specimen, the sac was large and overlaid Poupart's ligament. In this specimen there were found the largest lacunae vasorum of the entire series, 1,100 sq. mm. on the right (the side of the hernia) and 1,050 sq. mm. on the left. However, on the left side there was no evidence of hernia. Associated with this large right femoral hernia was an indirect left inguinal hernia. Five of the 6 sacs were on the right side. All sacs were empty.

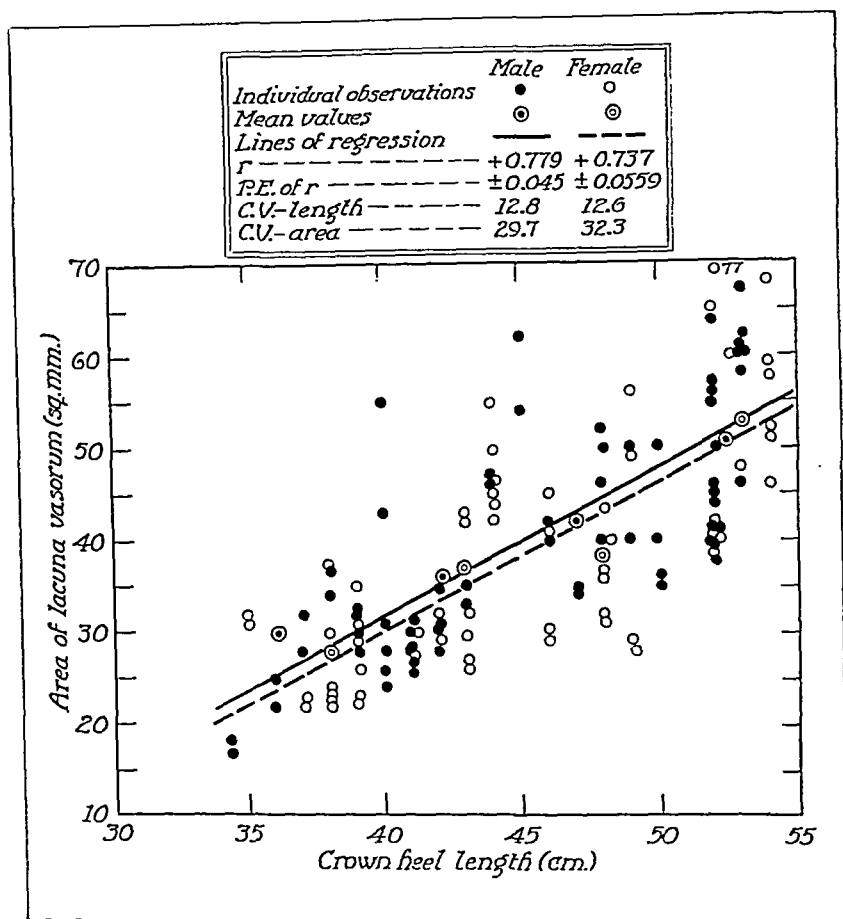


Fig. 4.—Field graph showing the area of the lacuna vasorum in premature and new-born infants according to the crown-heel length; the central tendency is indicated by regression lines.

There were also 7 cases with indirect inguinal hernial sacs; the one already described as associated with a femoral, 1 bilateral, 4 left-sided and 2 right-sided. None of these was very large. In 1 case bilateral obturator hernial sacs were also observed. No special search, however, was made for these in all cases examined. As far as is known, in no case was the subject aware that a hernia was present.

Of the 30 women examined, 8 gave a history of no pregnancies, 4 of only 1 pregnancy and 18 of 1 or more. In the latter group the



average number of children for each was 6 plus. The area of the lacuna vasorum in the group of 8 without children was 290 sq. mm., in the group with only 1 child it was 310 sq. mm., and in the group with more than 1 it was highest, 370 sq. mm. One of the group of 8 nulliparous women had one of the femoral peritoneal diverticula.

*Area of the Lacuna Vasorum According to Crown-Heel Length in Premature and New-Born Infants.*—The coefficient of correlation for

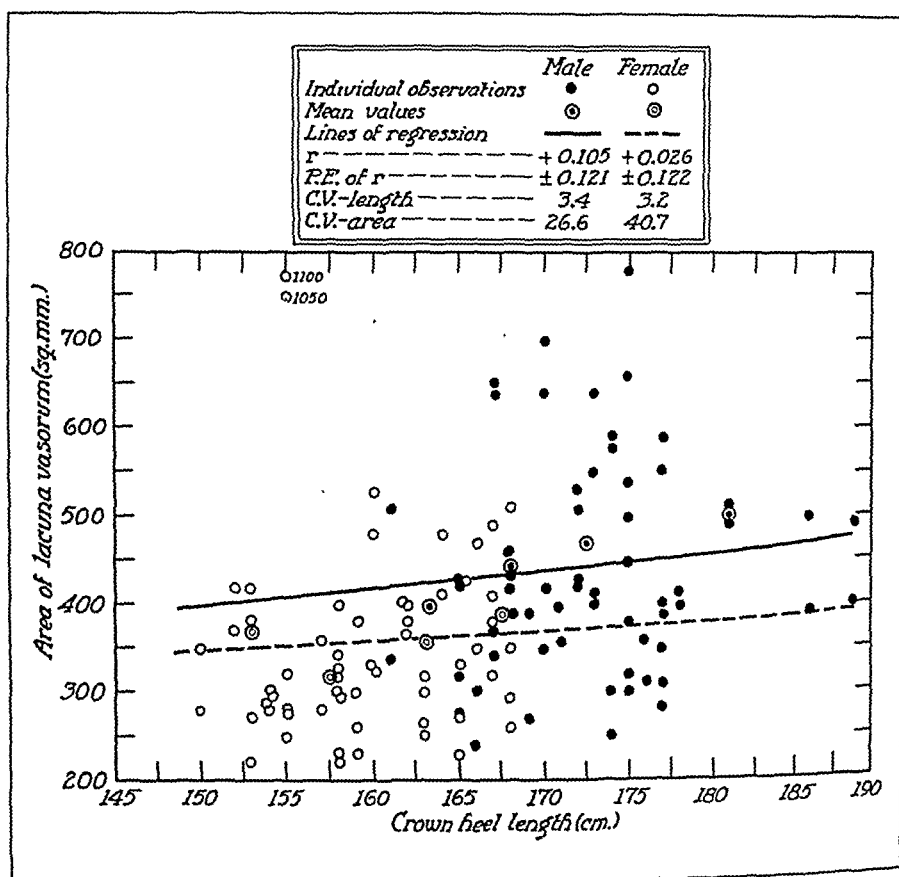


Fig. 5.—Field graph showing the area of the lacuna vasorum in adults according to crown-heel length; the central tendency is indicated by regression lines.

the males in this group was  $+0.779$  with a probable error of  $\pm 0.045$ , and for the females it was  $+0.737$  with a probable error of  $\pm 0.0559$ . This high correlation was demonstrated in figure 4.

*Area of the Lacuna Vasorum According to Crown-Heel Length in Adults.*—No correlation of significance could be demonstrated graphically or numerically in this group. The coefficient of correlation for the males was  $+0.105$  with a probable error of  $\pm 0.121$ , and for the females it was  $-0.026$  with a probable error of  $\pm 0.122$  (fig. 5).

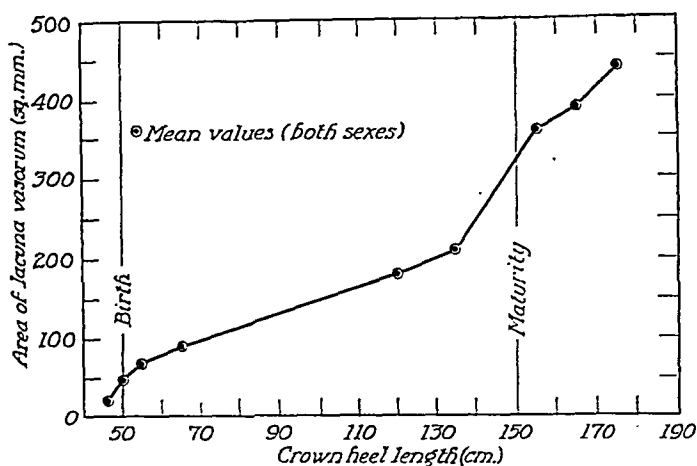


Fig. 6.—The area of the lacuna vasorum in premature and new-born infants, children and adults according to crown-heel length; the average of both sides and both sexes is shown.

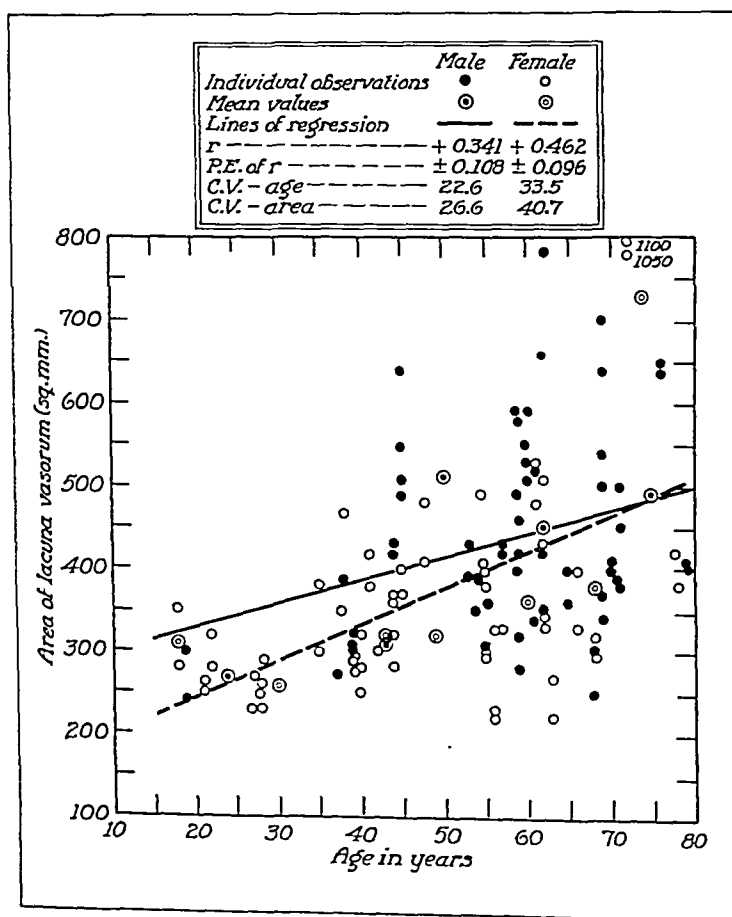


Fig. 7.—Field graph showing the area of the lacuna vasorum in adults according to age; the central tendency is indicated by regression lines.

In figure 6 it is apparent that when an average of all of the cases was taken for each of three long intervals (10 cm. crown-heel length) there was a definite increase in the area of the lacuna vasorum according to length; but it must also be remembered that this increase in size is probably accounted for by the fact that the larger persons are all males, and that the males have larger lacunae in proportion to length than do females.

*Area of the Lacuna Vasorum According to Age in Adults.*—A fair degree of correlation exists between the area of the lacuna vasorum and age, especially in the female group. The coefficient of correlation for the males was  $+0.341$  with a probable error of  $\pm 0.108$ , and for

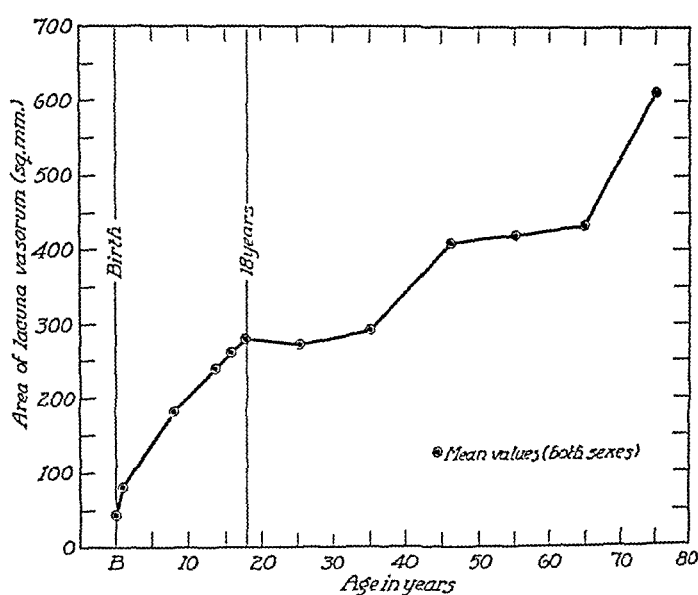


Fig. 8.—Area of the lacuna vasorum from birth to old age.

the females  $+0.462$  with a probable error of  $\pm 0.096$ . This correlation was further demonstrated in figure 6.

In figure 7 is shown the growth in size of the lacuna vasorum from birth to old age. Between the ages of 18 and 35, there is a flat area which may be of significance, although this again occurs between the ages of 45 and 65.

*Length of Poupart's Ligament According to Crown-Heel Length in Premature and New-Born Infants.*—There is good correlation between Poupart's ligament and length in this group. For the males the coefficient of correlation is  $+0.846$  with a probable error of  $\pm 0.032$ , and for the females it is  $+0.825$  with a probable error of  $\pm 0.039$ . Figure 9 shows this still further.

*Area of the Lacuna Vasorum According to Length of Poupart's Ligament in Premature and New-Born Infants.*—Again the correlation

is good. For the males it is  $+0.681$  with a probable error of  $\pm 0.0615$ , and for the females  $+0.70$  with a probable error of  $\pm 0.062$ . These facts are demonstrated in graphical form in figure 10.

*Length of Poupart's Ligament According to Crown-Heel Length in Adults.*—There is definite but not a great deal of correlation in this group. For the males the coefficient is  $+0.479$  with a probable error of  $\pm 0.094$ , while for the females it is  $+0.364$  with a probable error

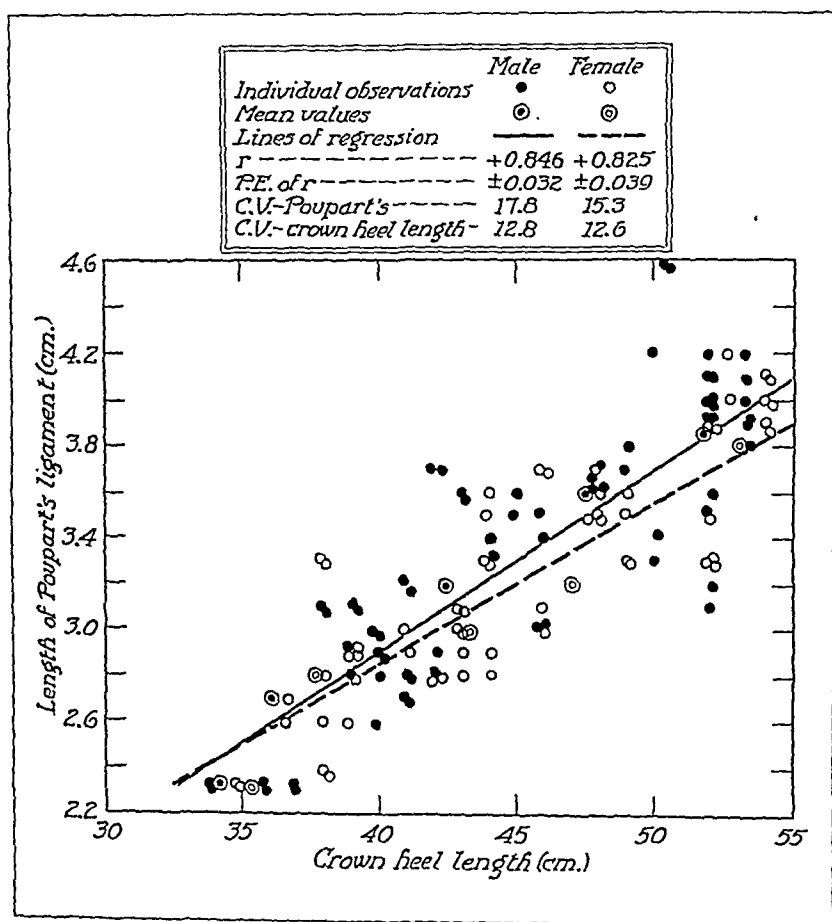


Fig. 9.—Field graph showing the length of Poupart's ligament in premature and new-born infants according to crown-heel length; the central tendency is indicated by regression lines.

of  $\pm 0.105$ . Figure 11 demonstrates still further the degree of correlation in each case.

*Area of Lacuna Vasorum According to Length of Poupart's Ligament in Adults.*—There was possibly a small amount of correlation in this group, the males showing a coefficient of correlation of  $+0.295$  with a probable error of  $\pm 0.111$ . The females showed none at all;

in fact, the coefficient was  $-0.101$  with a probable error of  $\pm 0.121$ . Figure 12 illustrates this lack of any definite correlation.

*Caliber of the Femoral Artery and Vein According to Crown-Heel Length in Premature and New-Born Infants.*—The correlation was good in both the artery and the vein. The coefficient of correlation between the caliber of the veins and crown-heel length for the males was  $+0.483$  with a probable error of  $\pm 0.089$ , while for the females

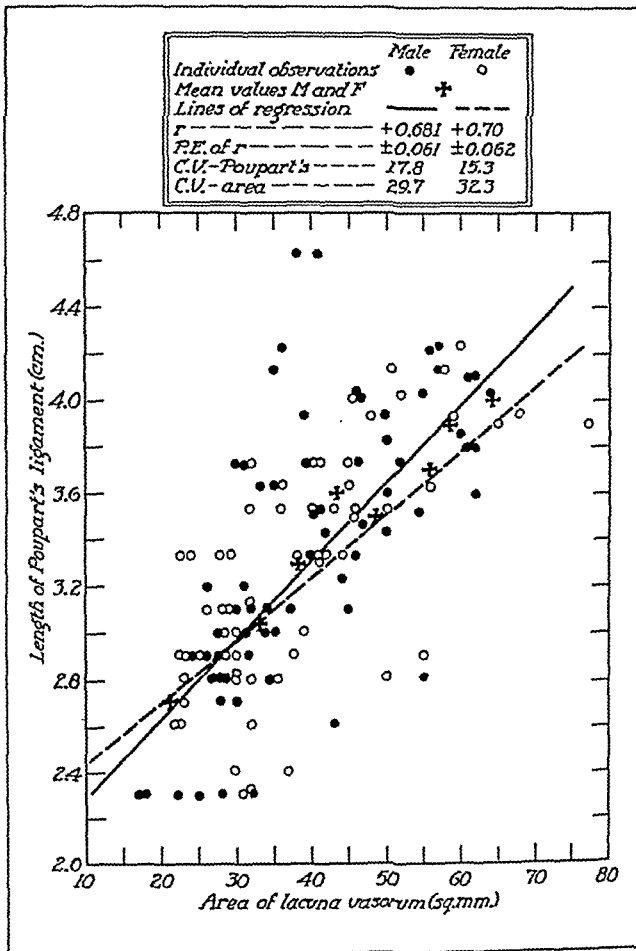


Fig. 10.—Field graph showing the area of lacuna vasorum in premature and new-born infants according to the length of Poupart's ligament; the central tendency is indicated by regression lines.

the coefficient was  $+0.463$  with a probable error of  $\pm 0.097$ . For the arteries, the coefficient was  $+0.547$  with a probable error of  $\pm 0.0818$  for the males, and for the females it was  $+0.565$  with a probable error of  $\pm 0.0847$ . This is further demonstrated in figure 13, which shows it graphically for the veins, and in figure 14 for the arteries.

*Caliber of the Femoral Vein According to the Area of the Lacuna Vasorum in Premature and New-Born Infants.*—There was fairly good

correlation in the males for these measurements, with a coefficient of  $+0.537$  and probable error of  $\pm 0.083$ ; but in the females the correlation was found to be barely present, the coefficient being  $+0.257$  with a probable error of  $\pm 0.116$ . Graphically, the correlation is definitely present and is illustrated in figure 15.

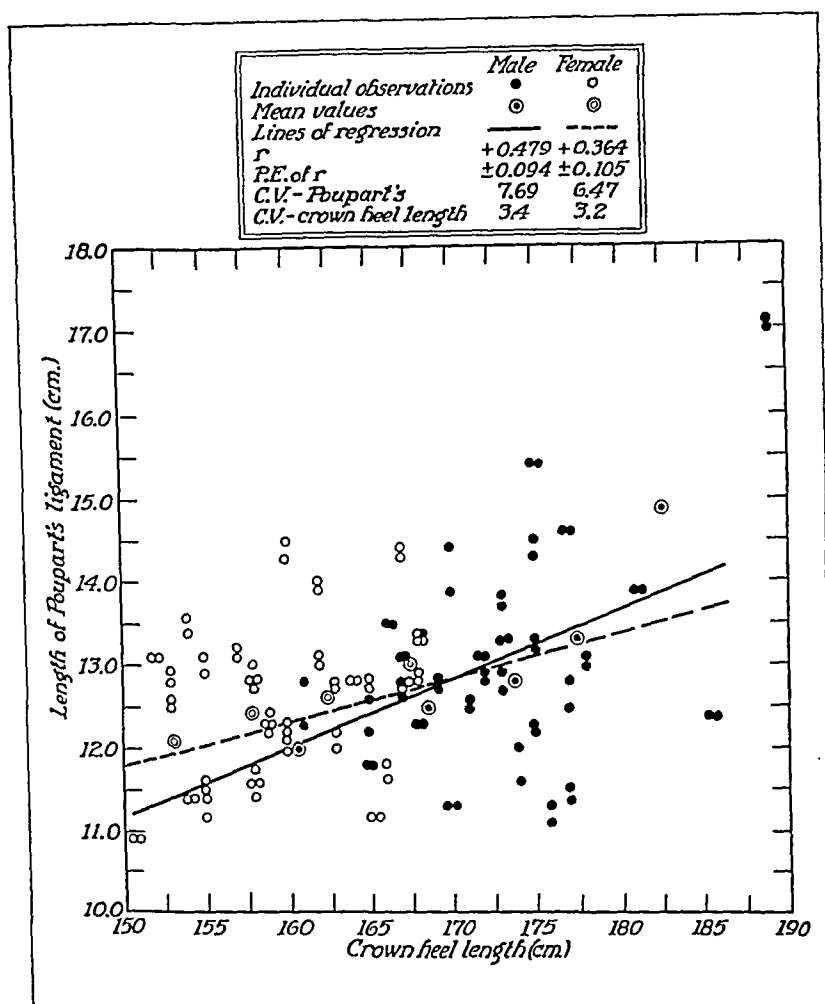


Fig. 11.—Field graph showing the length of Poupart's ligament in adults according to the crown-heel length; the central tendency is indicated by regression lines.

*Size of the Femoral Vein and Artery According to Age in Adults.*—There was no evidence of correlation between veins and age in adults. The coefficient for the males was  $+0.059$  with a probable error of  $\pm 0.122$ , and for the females  $+0.087$  with a probable error of  $\pm 0.121$ . In the arteries, however, there was fairly good correlation. The coefficient for the males was  $+0.447$  with a probable error of  $\pm 0.098$ , and for the females it was  $+0.421$  with a probable error of  $\pm 0.082$ . Figure

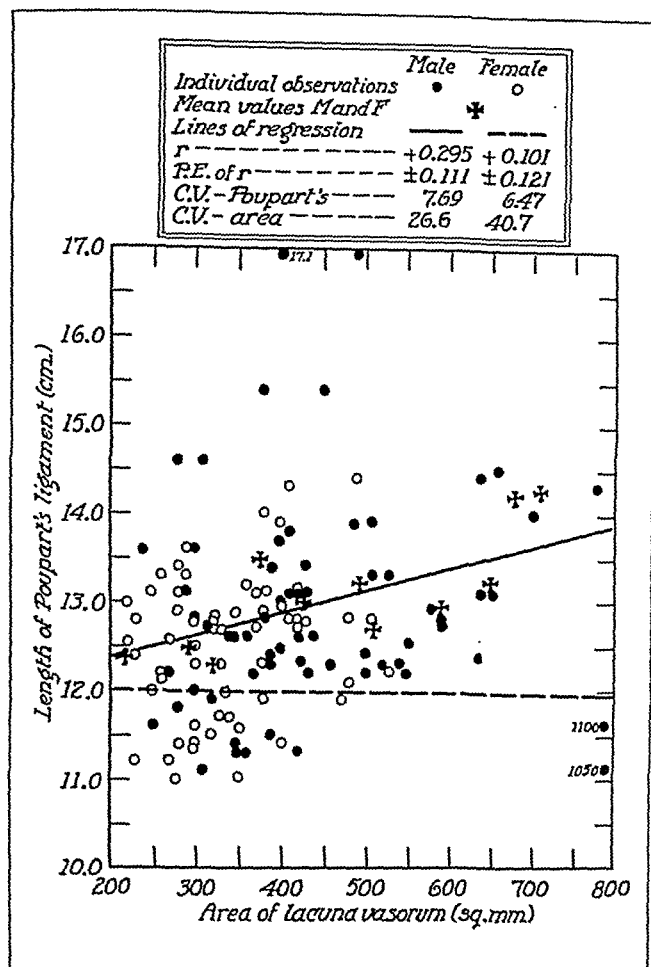


Fig. 12.—Field graph showing the area of the lacuna vasorum in adults according to the length of Poupart's ligament; the central tendency is indicated by regression lines.

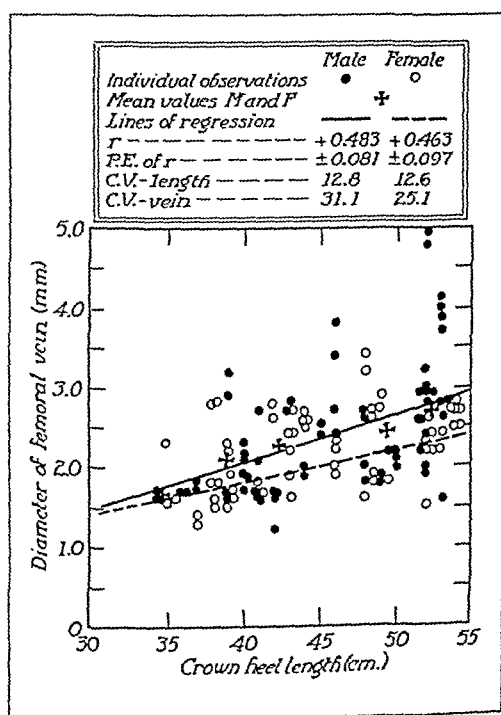


Fig. 13.—Field graph showing the caliber of the femoral vein in premature and new-born infants according to the crown-heel length; the central tendency is indicated by regression lines.

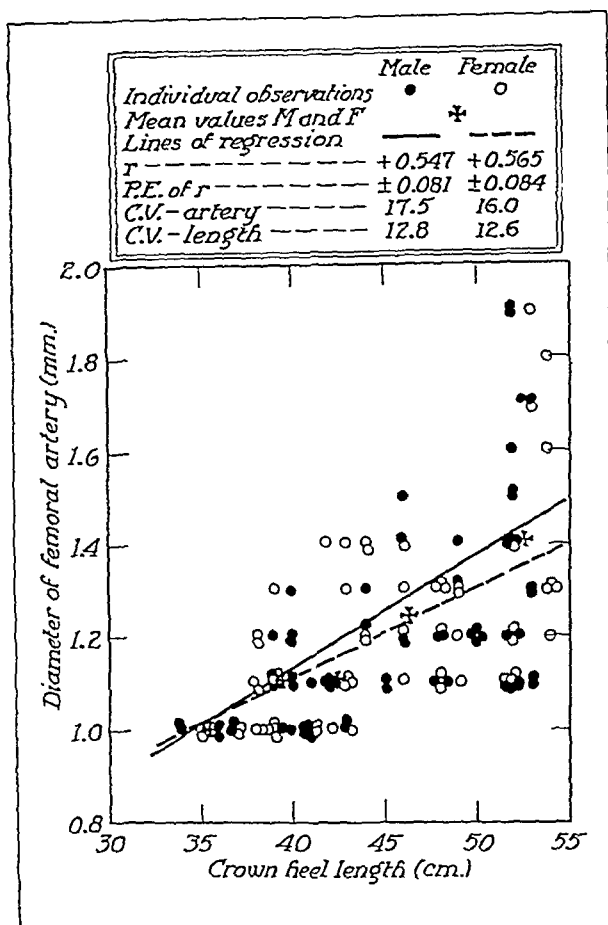


Fig. 14.—Field graph showing the caliber of the femoral artery in premature and in new-born infants according to the crown-heel length; the central tendency is indicated by regression lines.

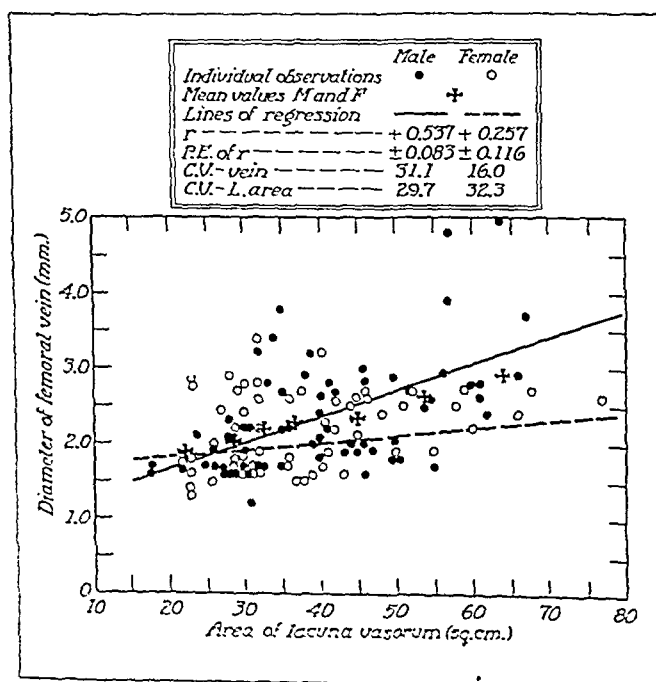


Fig. 15.—Field graph showing the area of the lacuna vasorum in premature and new-born infants according to the caliber of the femoral vein; the central tendency is indicated by regression lines.



16 illustrates these facts for the veins, while figure 17 does the same for the arteries.

*Size of Femoral Arteries According to Area of Lacuna Vasorum in Adults.*—There was no correlation found between the area of the lacuna vasorum and the femoral vein. The coefficient of correlation for the entire group was  $+0.088$  with a probable error of  $\pm 0.0606$ . In the

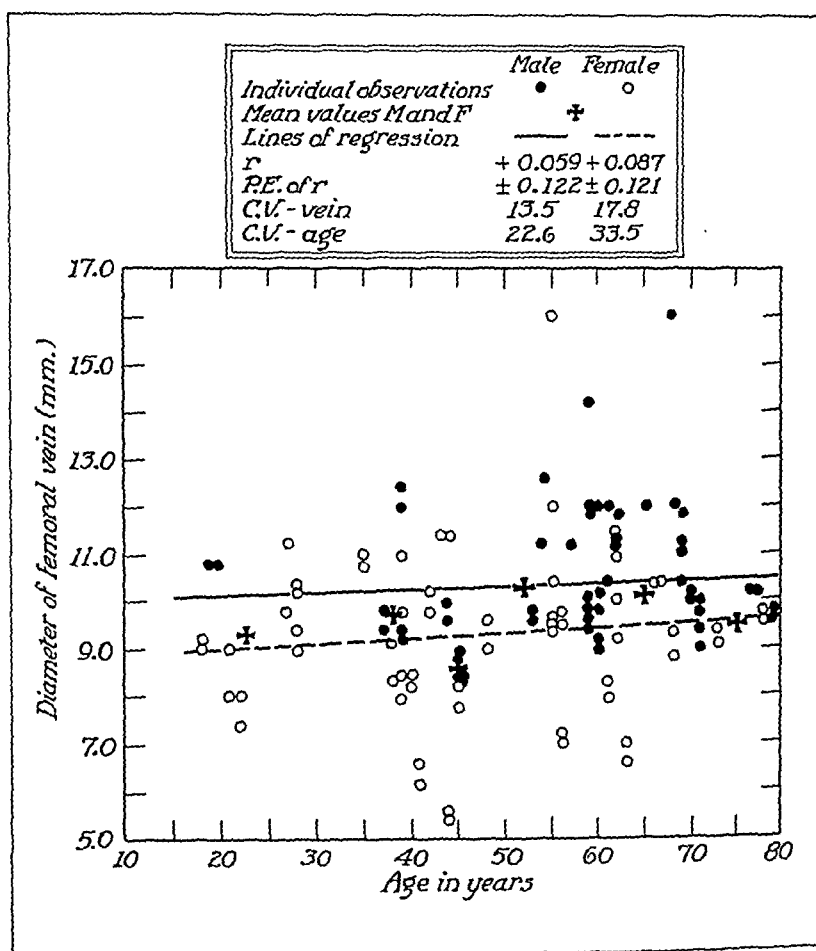


Fig. 16.—Field graph showing the caliber of the femoral vein in adults according to age; the central tendency is indicated by regression lines.

arteries there was some correlation present, with a coefficient of  $+0.250$  and probable error of  $\pm 0.056$ .

*Caliber of the Femoral Vessels According to Crown-Heel Length in Adults.*—No correlation was found in this group. The coefficient of correlation for males as to size of veins and crown-heel length was  $-0.197$  with a probable error of  $\pm 0.117$ , and for females it was  $+0.174$  with a probable error of  $\pm 0.118$ . In the arteries it was about the same, with a coefficient of correlation for the males of  $+0.041$  and probable error of  $\pm 0.122$ , and for the females  $+0.096$  with a

probable error of  $\pm 0.121$ . No graphs were made as it was evident that no correlation existed between the two.

*Thickness of the Walls of the Femoral Vessels According to Age in Adults.*—There was possibly some correlation present for the venous walls and good correlation for the arterial walls. For the males the coefficient of correlation for the arterial walls according to age was  $+0.330$  with a probable error of  $\pm 0.109$ , while for the females it

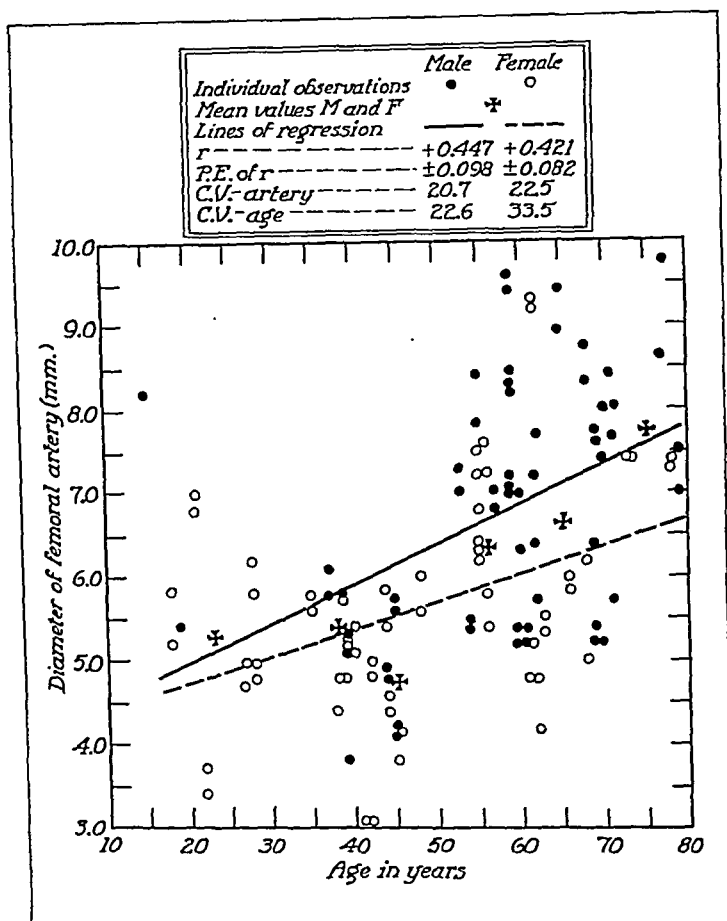


Fig. 17.—Field graph showing the caliber of the femoral artery in adults according to age; the central tendency is indicated by regression lines.

was  $+0.560$  with a probable error of  $\pm 0.084$ . In the venous walls the coefficient was  $+0.232$  with a probable error of  $\pm 0.115$  for the males, and  $+0.443$  with a probable error of  $\pm 0.093$  for the females. Figure 18 demonstrates the foregoing figures for the arteries. No graphic representation was made for the veins.

*Potential Space Available for the Development of Femoral Hernia.*—When the sum of the cross-section areas of the two femoral vessels are subtracted from the area of the lacuna vasorum, the available space

left is larger for males than for females. For males, this was 451 sq. mm. minus 173.9 sq. mm., or 277.1 sq. mm.; and for females, it amounted to 362.1 sq. mm. minus 133.6 sq. mm., or 228.5 sq. mm., a difference of about 50 sq. mm.

#### COMMENT ON CLINICAL AND ANATOMIC FINDINGS

From this and other clinical studies the following outstanding facts present themselves. Femoral hernias are relatively uncommon before

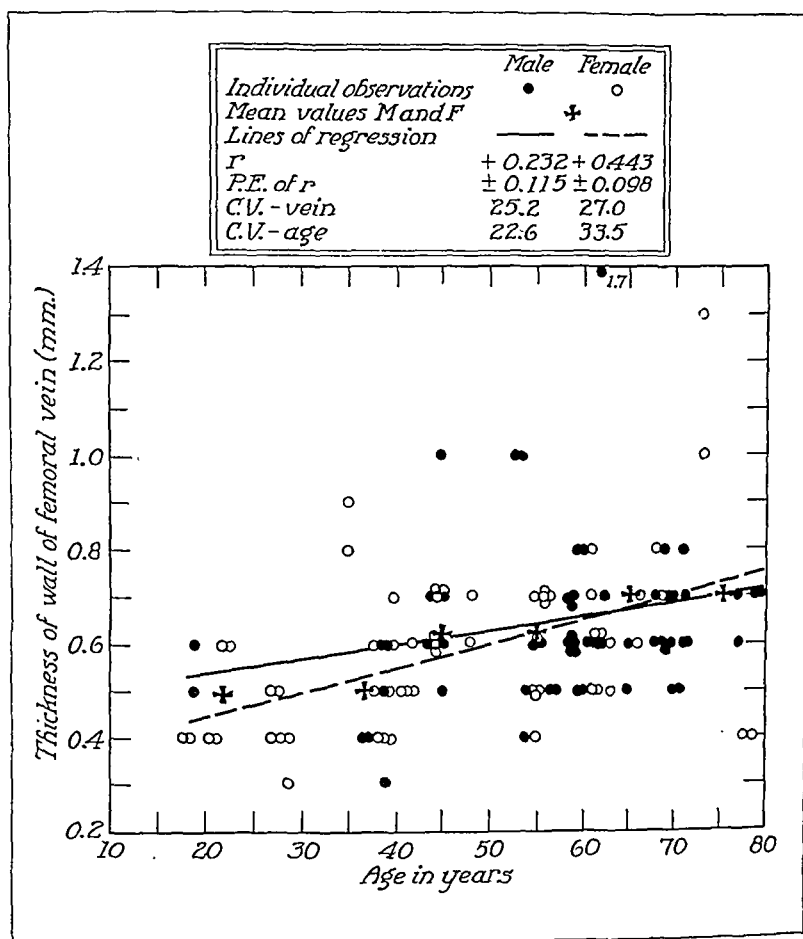


Fig. 18.—Field graph showing the thickness of the walls of the femoral vein in adults according to age; the central tendency is indicated by regression lines.

the age of 20 and probably have never been seen before the age of 2. They increase in frequency with age. Females afflicted outnumber males, and mothers, the childless. Heavy manual labor, the presence of asthma, chronic cough or debilitating diseases often are factors present in the appearance, if not in the original formation, of this type of hernia. Femoral hernia is eight times more liable to become

strangulated than inguinal hernia. A large number of the sacs seen at operation are empty. Most of them are small even when they contain omentum or bowel. When abdominal contents are present, they are frequently strangulated. Normal bowel was not present in any of the four hernial sacs in our series; all were strangulated. Most sacs are surrounded by a definite layer of fat. Recurrences following hernial repair, including removal of the sac, are common.

Anatomic findings demonstrate the following facts: Many peritoneal diverticula are found in adult bodies examined after death, which were unrecognized by the patient or physician during life. As a rule, all are found to be empty. There are as many of these pouches in males as in females. No femoral diverticula were ever found in otherwise normal new-born infants.

Women who have borne children are seen more often with femoral hernia clinically, probably because of the added strain occurring during labor which forces omentum or bowel into the sac, which has already been formed, and thereby brings its presence to the attention of the patient. In dead bodies studied, the incidence of femoral hernia sacs is the same in both sexes. The fact that the lacuna vasorum increases its area with age doubtless is a factor in the increased frequency of these hernia in the later decades of life. This increase is undoubtedly due to the relaxation of the ligaments, fascia and muscles, which occurs at this time.

Poupart's ligament is shorter in the female than in the male. The foramen vasorum is smaller in the female than in the male, even when considered proportionately according to size. The caliber of the femoral vessels is also smaller in women than in men. The size of the femoral ring (or, to be more exact, the area of the space available for the development of a femoral hernia) calculated by subtracting the diameter of the cross-section area of the two vessels from the total area of the lacuna vasorum is also smaller in females.

The lacuna vasorum increases in size with age as do the femoral arteries. This starts in early fetal life and continues to old age. The femoral vein shows similar correlation until adult life is reached; thereafter, the caliber varies with changes in weight and height.

Because femoral hernial sacs are frequently found in adult bodies, especially in the later years of life, and never in new-born infants, the conclusion must be that these diverticula are acquired. They are usually empty, but when abdominal organs once enter the sac they frequently become strangulated. It seems highly improbable that an organ that cannot be easily reduced back into the abdominal cavity could originally have much influenced the formation of that sac.

Traction on the peritoneum drawing it down through the lacuna vasorum is the most logical reason for the formation of all femoral hernial sacs, but what produces this traction is extremely difficult to explain. Abnormal gubernacular bands have been considered by some to be the cause, but even if the gubernaculum could influence the descent of the peritoneum it would do this extremely early in life and not after birth. The other possibility lies in the covering of fat that is present normally in the crural region and is practically always found covering the fundus of the sacs. How fat can do this no one has as yet explained, but a similar situation is probably present in the formation of the hernia through the vascular foramina of the linea alba, and it seems reasonable that it can occur in the femoral region as well.

#### CONCLUSIONS

1. Femoral hernial sacs are never congenital. They are always acquired and are produced by traction and not by pressure.

2. Males have as many femoral peritoneal diverticula as females, but clinically femoral hernia are found twice as often in women as in men.

3. The lacuna vasorum increases in size in both sexes from fetal life to old age. This enlargement of the lacuna vasorum favors the production of femoral hernia because it allows the force of traction to act to better advantage.

4. The lacuna vasorum is smaller in the female than in the male.

5. Poupart's ligament is shorter in females than males.

6. There is very little, if any, correlation between the size of the lacuna vasorum and the length of Poupart's ligament in adults. In fetal life and early infancy there is a high correlation.

7. The femoral artery increases in caliber from fetal life to old age.

8. The femoral vein increases in caliber up to adult life and then varies according to other factors such as height and weight.

9. The walls of the femoral artery and vein increase in thickness with age.

10. There is no correlation between the size of the lacuna vasorum and the size of the vessels in adults; during fetal life and early infancy this correlation is good.

11. Extirpation of the hernial sac with adequate closure of the femoral orifice offers the patient the best hope of permanent cure.

12. The available space for the development of a femoral hernia is smaller in the female than in the male; that is, the difference between the sum of the areas of the two femoral vessels subtracted from the total area of the lacuna vasorum, is greater in males than it is in females.

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# CHANGES IN THE WALL OF THE BLADDER SECONDARY TO PROSTATIC OBSTRUCTION

THEIR SIGNIFICANCE IN PROSTATIC SURGERY

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A consideration of prostatic obstruction and the treatment for it entails: first, an analysis of the variation from normal function of the posterior urethra, internal sphincter, trigon and wall of the bladder; second, a consideration of how the type and location (relative to the internal sphincter) of the obstructing mass may bring about such variation and so specifically alter the action of these parts as to account for the marked dissimilarity in individual cases with regard to symptoms, infection, both local and generalized, and renal and secondary systemic changes.

If the onset is with prostatitis in early middle life scar tissue formation followed by adenomatous changes occurs, and symptoms of irritability precede those of obstruction. In this type, the scar tissue change is frequently the primary obstructing factor, associated or not with later adenomatous changes. The second classification includes those cases in which there are adenomatous changes with secondary infection induced by the blocked acini. In both types, the obstructive symptoms depend entirely on the shape and size of the obstruction and its location, particularly as to whether it is intra-urethral, at the internal sphincter or unusually intracystic. On account of this variability in location, rectal examination may give an erroneous idea of the size of the obstructing prostate; if located deep in the urethra, the prostate will seem much larger to the examining finger than if it were located high on the internal sphincter. As no two prostates were ever alike in size, shape, location, consistency and degree of infection,<sup>1</sup> the proper diagnosis in, and the method of handling, an individual case depends on determining its exact status in each of these particulars. For example, a small prostate with scar tissue and with a very small intra-urethral

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Read before the North Central Branch of the American Urological Association, St. Paul, Minn., Oct. 29, 1931.

1. Randall, Alexander: *Surgical Pathology of Prostatic Obstruction*, Baltimore, Williams & Wilkins Company, 1931.

adenomatous mass may block completely, while a large, intracystic, adenomatous prostate may be of little clinical importance, except for the associated infection.

From the standpoint under discussion here, cases of prostatic obstruction may be divided into those in which the obstruction gains control early in the course of the disease and those in which the wall of the bladder (by anatomic compensation) retains its ascendancy over the obstruction.<sup>2</sup> In the second type, the obstruction is imperfect and develops slowly, and the wall of the bladder compensates readily on relief of the acute dilatation. This accounts for the disappearance of a residual urine after catheterization in certain obstructed bladders. It is in this type, also, that diverticula<sup>3</sup> frequently develop. The first type is one in which the obstruction defeats the wall of the bladder early in the course of the disease. The more sudden the onset of the obstruction, the less the change in the wall up to the time relief becomes necessary. It is possible to classify the degree of change in the wall that has been brought about by the individual prostate, and as the bladder is the intermediary in renal damage and infection, one can determine best the most suitable individual treatment by studying alterations in the function of the wall of the bladder.

The first degree of change in the wall is a physiologic hypertrophy in which sensation is, to a certain extent, in direct ratio to intracystic pressure. In this type, on account of the increase in the initial force of the contraction, one expects some frequency and urgency of urination, with or without slightly diminished force of stream. Should an infection occur at this stage, it would be much more violent than in a normal bladder, owing to the trauma of the too forceful contraction of the wall of the bladder and its internal sphincter. Associated with this change in the wall of the bladder and progressing as it does, with the increased duration and type of obstruction and infection, comes increased strength and irritability of the internal sphincter. The trigonal muscle,<sup>4</sup> which lowers the floor in association with the action of the arcuate fibers, becomes hyperplastic in an attempt to depress the spastic, fibrous or adenomatous type of hindrance to the internal sphincter. The posterior urethra is elongated, made resistant to dilatation by the urinary stream and less mobile to the pump handle-like action given it by the anterior portion of the levator ani muscle.<sup>5</sup>

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The second degree of change produced by continued obstruction with increasing compensation is an early physiologic decompensation. At this point the obstruction is in the ascendancy in that it has continued its resistance past the point for which the wall of the bladder can compensate, and some residual urine has accumulated. This change is in the nature of a physiologic nerve block or pressure anesthesia,<sup>6</sup> a provision to deal with the increased intracystic pressure. The symptoms are now definitely those of obstruction, but a retention catheter even at this time, by increasing the irritability of the posterior urethra, emptying the bladder and so thickening the wall, can temporarily reduce or remove the residual urine. However, in certain types it may increase the block by traumatizing the obstructing surfaces. Such a situation would be most unfortunate, as any infection in the face of an increased block in the thickened wall tends to dissemination through the blood stream, directly up the ureteral<sup>7</sup> lumen or via the lymphatics.

The third degree is an early anatomic decompensation, that is, a beginning thinning of the peak of anatomic compensation of the wall. This is due to long-continued increase in capacity, fibrous tissue change and increased and continued pressure anesthesia. Decompensation may continue to cellule and diverticulum formation, and such a bladder, in the cystogram, often shows the typical conical allantoic weakness with cellules or diverticula and deep trabeculations about the base.<sup>3</sup> The symptoms of this degree are those of greater dysuria, the frequency and urgency either having passed, owing to the decompensated wall, or when persisting, causing very little distress. The amount of residual urine increases with decompensation.

The fourth and greatest degree of change in the wall of the bladder, myogenic decompensation, is the one in which there is a paradoxical incontinence; that is, all the elasticity of the wall has been lost. This may develop with or without associated infection. In a large majority of cases, infection has occurred, and its onset and progress may be traced by an analysis of the symptoms throughout the past years. It will usually be found that early in the course of the disease marked frequency, urgency, etc., developed and lasted for some time, indicating a sudden increase in irritability and so increased contraction and power of the wall of the bladder. A long-standing infection markedly increases the degree of decompensation.

The more sudden the onset of complete obstruction, the less marked, at the time, will be the change in the wall of the bladder, the infection and the damage to renal function. The more gradual the obstruction, the greater the change and the greater the percentage showing associ-

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ated pathologic conditions. The direct<sup>8</sup> or involuntary nerve reflex, the altered circulation, the type of ureteral orifice<sup>7</sup> the kink of the ureter over the vas deferens,<sup>9</sup> the descent of the base of the wall of the bladder,<sup>9</sup> the hypertrophy of the musculature closing off the intramural ureter,<sup>10</sup> all, in their influence on renal damage, are individual considerations in each type of obstruction, and all are associated with altered function of the wall of the bladder.

Cystometrograms that graph the changes in the wall of the bladder are presented in further explanation. The central nervous system was normal in all cases considered here.<sup>11</sup> While specific examples of the various stages of change are given, these cystometrograms can, in no way, represent other than the individual cases. But through an understanding of their interpretation on the basis of the interrelationship of pressure, capacity and sensation,<sup>12</sup> one can visualize the status of the wall of any bladder, that is, the mechanics bringing about local symptoms, as well as possible secondary general influences that may enter into the surgical handling of a specific case.

#### CYSTOMETROGRAM 1: "NORMAL"

Cystometrogram 1 shows a gradual increase in involuntary pressure with *correctly placed sensations*, and a *moderately high voluntary pressure* with good capacity and with a sphincter control in excess of requirements, as shown by the fact that there is no leakage about the catheter. The second curve is slightly higher and the capacity less than the first, which is characteristic of a great percentage of normal bladders and is due to stimulation of the smooth muscle by the rapid stretching and relaxation of the first filling.

#### CYSTOMETROGRAM 2: EARLY STAGE OF COMPENSATION (PHYSIOLOGIC HYPERTROPHY) OF WALL OF BLADDER

Cystometrogram 2 represents the first degree of change in an obstructed bladder in that the capacity is slightly decreased and the pressures raised, the initial involuntary contraction of the wall of the bladder being especially significant. Sensations remain normally placed. In a bladder showing an early compensation type of curve, one expects

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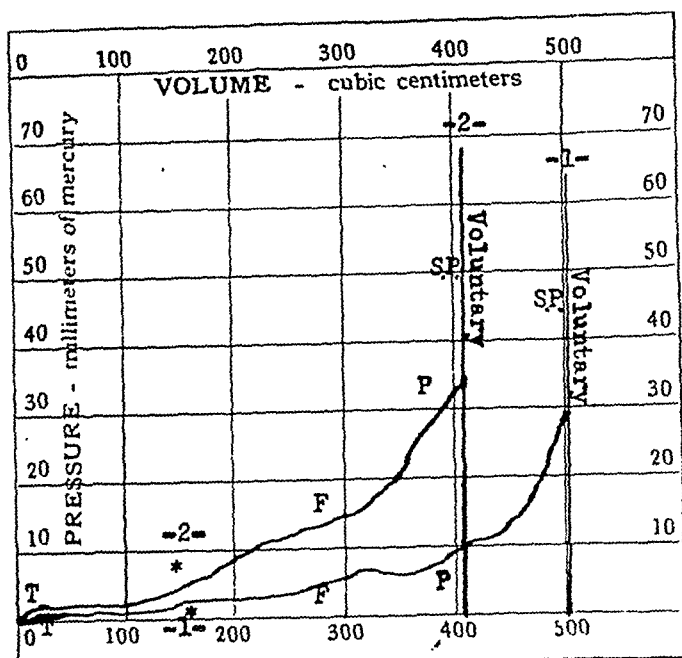


Chart 1.—Cystometrogram of a normal person (F). The terms abbreviated in this and subsequent charts are: Temperature (T); first desire to void (\*); fulness (F); pain (P), and severe pain (S.P.). A gradual increase in involuntary pressure, correctly placed sensations and a moderately high voluntary pressure are shown. The patient had good capacity with a sphincter control in excess of requirements, as shown by the fact that there was no leakage about the catheter.

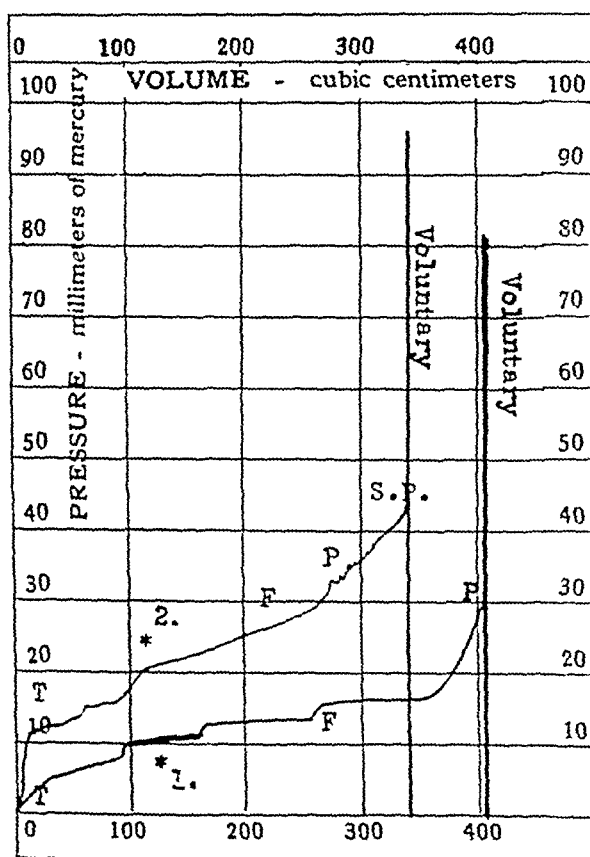


Chart 2.—Early stage of compensation of the wall of the bladder (patient F.S.)

some frequency and urgency, as, when the stimulation to void occurs, the contraction is more abrupt than normal. This abruptness is assisted reflexly by the irritability of the posterior urethra (pudic nerve).<sup>13</sup> Oscillations or toothlike variations in the smooth filling are caused by a transmission of the pump pressure through a fixed wall of the bladder, back to the mercury manometer.<sup>14</sup> They indicate, therefore, a spastic musculature. Infection without hypertrophy will not produce these oscillations. Normally, the musculature receives the inflowing fluid so smoothly that the pump pressure is absorbed by the elasticity of the wall of the bladder and not transmitted to the manometer.

#### CYSTOMETROGRAM 3A: ACUTE CYSTITIS

Cystometrogram 3A shows a very high voluntary and involuntary pressure, increased sensations with small capacity and no leakage. It is obvious that such a bladder would produce urgency, frequency and, probably, terminal pain and bleeding, that is, symptoms of irritation plus increased power. The increased power is due to the reflex contraction of the wall and the irritable mucosa resenting and expelling small amounts of fluid, which, by lessening the storage requirement, is a factor in producing greater frequency through greater contraction of the wall of the bladder by its diminishing capacity—a vicious circle. Should such a change occur in a markedly hypertrophic bladder, one can readily see why the residual urine would disappear and increased irritative symptoms supersede.

#### CYSTOMETROGRAM 3B: SUBACUTE URETHRITIS

In contrast with cystometrogram 3A, cystometrogram 3B shows urethritis without cystitis, low voluntary and involuntary pressure with increased irritability, and inhibition of the wall of the bladder protective to the hyperirritable urethra. In some instances, even a negative pressure is obtained, showing the psychic control over the involuntary wall of the bladder.<sup>15</sup> Leakage about the catheter is very unlikely to occur, even with severe pain of overdistention, which, characteristically, here occurs with a low pressure and small capacity. The same degree of pain in an acute cystitis occurring with an excessively high pressure and similar capacity would tend to show leakage about the catheter in a certain percentage of cases in the effort of the mucosa of the bladder

13. Barrington, F. W. F.: *Proc. Roy. Soc. Med. (Sect. Urol.)* 20:22, 1927. Schwarz, O.: *Ztschr. f. urol. Chir.* 10:167, 1922. Ranson, S. W.: *The Anatomy of the Nervous System*, ed. 3, Philadelphia, W. B. Saunders Company, 1927, p. 336. Learmouth, J. L., and Braasch, W. F.: *Surg., Gynec. & Obst.* 46:221, 1928.

14. Rose, D. K., and Rollins, P. R.: *Pyelonephritis in Pregnancy: Its Treatment and Prevention Based on Cystometric Conclusions*, *J. A. M. A.* 96:235 (Jan. 24) 1931.

15. Rose (footnote 2, first reference).

to rid itself of the fluid. Such an inhibition may lower the pressure in a wall of known compensation and so markedly alter the picture (see cystometrogram 5). The influence of urethritis must therefore be borne in mind in the interpretation of all types of cystometrograms.

CYSTOMETROGRAM 4: EARLY STAGE OF DECOMPENSATION (PHYSIOLOGIC)  
OF WALL OF BLADDER

Cystometrogram 4 shows a large capacity with low voluntary and involuntary pressure. The decreased sensations are physiologic, that is,

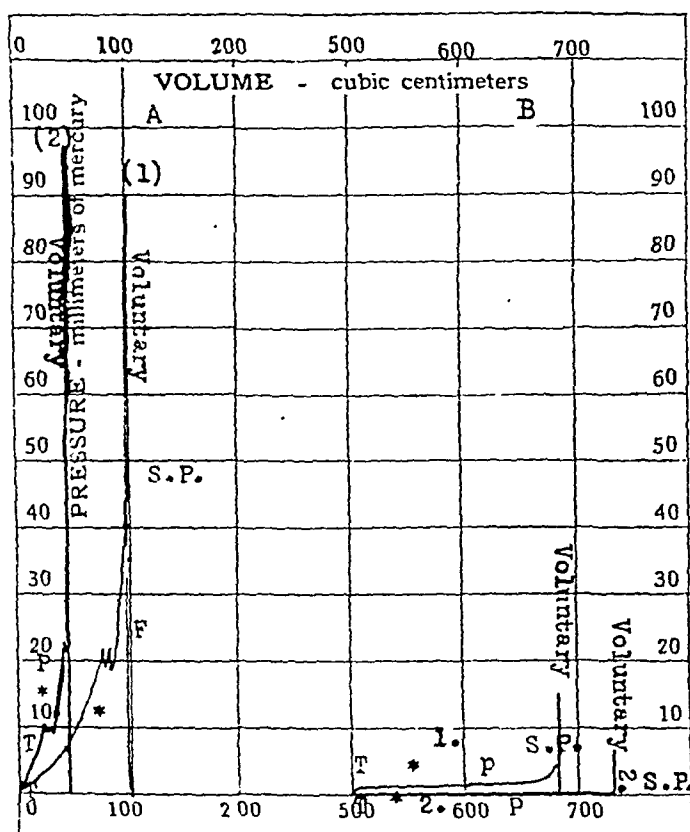


Chart 3.—A, acute cystitis (patient T. F.) ; B, subacute urethritis (patient F. F.).

of the pressure anesthesia type. At this early stage in the decompensation of the wall of the bladder, anatomic compensation is just below its peak. The patient, aged 50, carried 750 cc. of residual urine, which was not infected. His symptoms were those of marked obstruction without irritation. As he had never been catheterized, a catheter was attached to the manometer and the full bladder recorded 30 mm. of mercury (marked "A" on the chart). The bladder was then emptied, and cystometrogram 5 was made. "First desire to void" (\*) in curve 1 occurred at 350 cc. and in curve 2 at 250 cc. (normal is about 150 cc.).



With this exception, the sensations of fulness and pain were normally placed for the type of curve. The occasional abrupt, single rises are due to the thickened wall, which contracts reflexly with the slight discomfort of the catheter. Note that the severe pain (*S. P.*) of over-distention does not occur up to 600 cc. filling. Taken as a whole, this cystometrogram shows a slightly weakened wall and yet one that is far from being thinned. Delayed "first desire to void" in association with a compensated wall accounts, in part, for the lower pressure and rather large capacity.

Following this cystometrogram, rather than put in a retention catheter, the patient was watched carefully and catheterized every six to eight hours. Twenty-four hours later cystometrogram 5 was made.

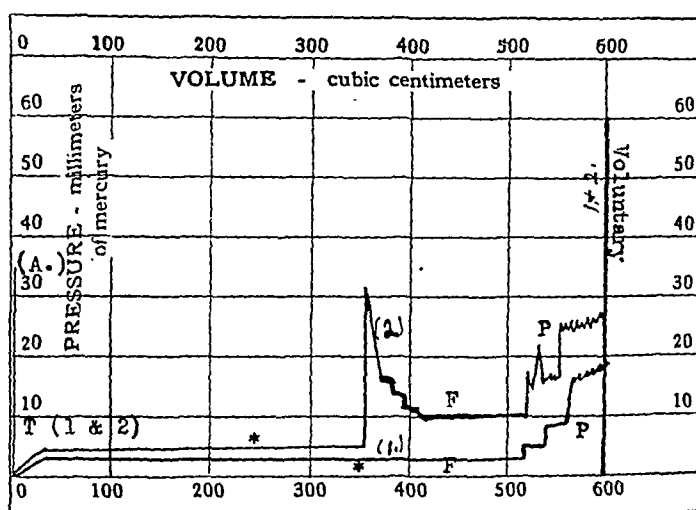


Chart 4.—Early stage of decompensation of the wall of the bladder (patient E. H. [X]). As this patient had never been catheterized, a catheter was attached to the manometer, and the full bladder recorded 30 mm. of mercury (marked *A*). The bladder was then emptied and the cystometrogram made.

#### CYSTOMETROGRAM 5: CATHETER COMPENSATION

As compared with cystometrogram 4, cystometrogram 5 immediately shows the effect of catheterization in the decreased capacity, much higher pressure, increased sensations and spasticity of the wall of the bladder, as shown by the oscillations in curve 2. A retention catheter, in this type of compensated wall, would produce a curve not unlike that of cystometrogram 3A, that is, a very abrupt rise, depending, of course, on the duration of the retention catheter and the associated infection. In this (5) one has, in curve 1, a low pressure following the base line to 170 cc., at which point an abrupt rise occurs. This is due, in part, to an associated urethritis, produced by the intermittent catheterization, temporarily inhibiting the wall of the bladder (see cystometrogram 3B). While the full bladder was emptied just before

making curve 1, its filling had been so gradual that the stimulating effect of a rapid stretching of the smooth muscle was absent, but this effect was produced by the first cystometric filling and explains the rather abrupt rise in pressure with the second filling, as well as the higher voluntary pressure. It is therefore a catheter compensation in an anatomically thickened wall associated with subacute urethritis produced by intermittent catheterization.

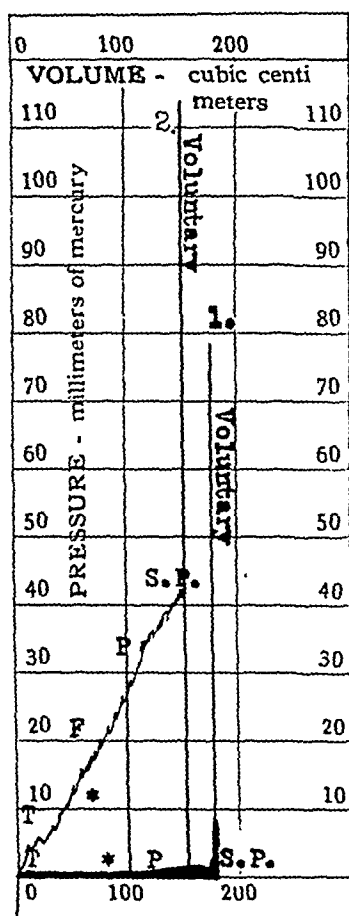


Chart 5.—Catheter compensation (patient E. H. [X]).

#### CYSTOMETROGRAM 6: ACUTE DECOMPENSATION OF WALL OF BLADDER

Cystometrogram 6 shows a large capacity and lowered voluntary and involuntary pressure, with slightly delayed sensations. The patient had retention of urine (1,300 cc. infected with *Bacillus coli*), enlargement of the prostate, with marked secondary anemia, and an inguinal hernia, which was a recent development in association with straining on urination. The second curve, being higher than the first, favors a normal central nervous system, which is an important point in considering such a large capacity of the bladder. Associated with this is

the interesting fact that his first failure to urinate occurred only a few hours before examination. Undoubtedly, from the history, an acute cystitis had developed three years previously, and, at that time, with irritation of the already thickened wall of the bladder, there had been periods of marked frequency, urgency with incontinence of urine, and some terminal pain with bleeding. This infection subsided, and the strength of the wall of the bladder started on its downward path once more, but it was still able to overcome the particular type of obstruction, only to fail in acute decompensation on the day the cystometrogram was done.

#### CYSTOMETROGRAM 7: LATE DECOMPENSATION OF WALL OF BLADDER

Cystometrogram 7 shows only one complete filling curve, the second being partial. Curve 1 shows normal or diminished capacity with

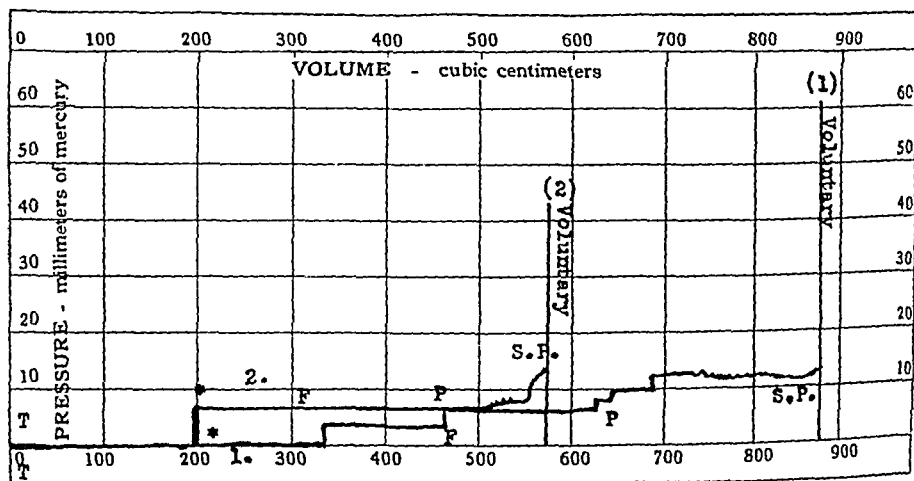


Chart 6.—Acute decompensation of the wall of the bladder (patient W. A. D.).

unusually high voluntary and involuntary pressure. The involuntary pressure is paradoxical, the effect of the catheter, in that it is abruptly high after an initial low pressure to 170 cc., with which there is no "first desire to void" (\*). This initial low pressure indicates myogenic decompensation, and this is confirmed by curve 2. Sensations are delayed by prolonged pressure anesthesia influenced by chronic inflammatory changes. The patient had 400 cc. of residual urine, had been on self-catheterization and had been markedly infected (*B. coli*) for years. His symptoms were those of obstruction with moderate irritation when the bladder was markedly overdistended. Cystoscopic examination showed three large diverticula, coarse trabeculations and many shallow and a few ballooning cellules.<sup>3</sup> The prostate and diverticula were removed in a two stage suprapubic operation, with satisfactory results. The results of neurologic examinations both before and after operation were entirely negative.

Without catheterization this curve would have been entirely different, that is, it would have shown large capacity, lower pressure and greater delay in sensation (\*). The initial flat curve with abrupt rise, delayed "first desire to void" with an oscillating type of involuntary pressure with high voluntary pressure, together with the long history of catheterization, acute blocks with relief, and a remaining residual of 400 cc., show the cystometrogram to be that of a late decompensation of the wall of the bladder with catheter influence.

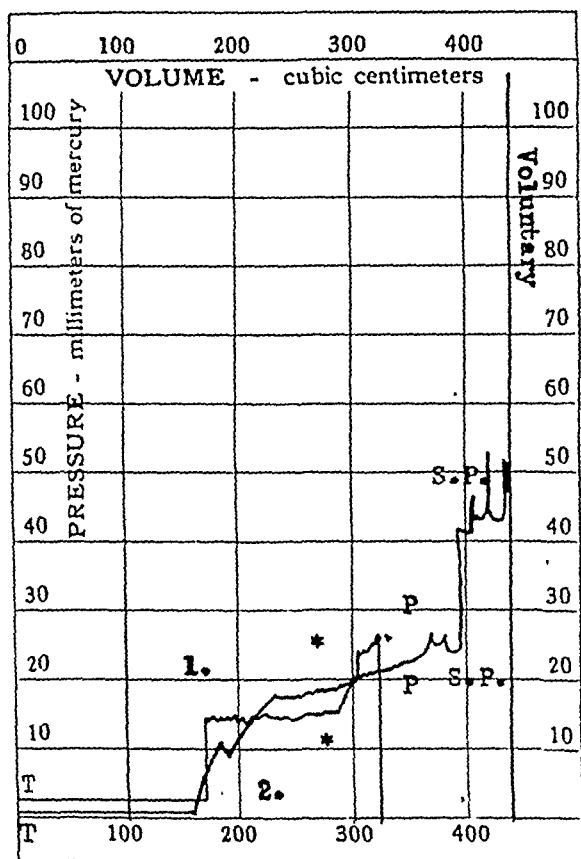


Chart 7.—Late decompensation of the wall of the bladder (patient J. G.).

#### SUMMARY WITH SURGICAL CONSIDERATIONS

Prostatic obstruction, therefore, brings about changes in the wall of the bladder depending on its size, shape, position, location, degree of infection and rapidity of development. These changes may be arrested at any stage of compensation or of decompensation provided the balance of power between prostatic resistance and expulsive force of the wall remains in favor of the latter. Compensation may be effected, depending on the degree of obstruction and decompensation, by means of a retention catheter or even, at times, by a single catheterization. An acute infection under similar conditions may bring about a compensation.

The surgical considerations are that a physiologically hypertrophied wall will attempt to force the retention catheter out and so cause pain, exacerbate and tend to generalize infection by trauma, and endanger the kidneys (infection or back pressure change).<sup>10</sup> If this trauma occurs and with it the compensated bladder wall is still unable to overcome the obstruction, the vicious circle of infection plus trauma without free drainage is initiated and continues to the point at which volume of fluid overcomes the forceful contraction of the wall. Catheterization is then increasingly dangerous.<sup>16</sup> The exception to bad results must be due, in these cases, to a sufficient drainage, to a low compensation in the wall of the bladder, or to the fact that the organisms are of low virulence. This degree of physiologic hypertrophy can be recognized clinically by the history of moderate obstructive symptoms with occasional complete obstruction, relieved by catheterization. In this, one must differentiate the obstruction of a distended wall (drinking too much, unable to void at an early warning, etc.) from one in which repeated early attempts to void were futile, with secondary, so to speak, dilatation thinning of the wall. In this type, from the standpoint of the influence of the wall of the bladder alone, absence of an acute or subacute infection indicates a one stage removal with free and uninterrupted drainage. The type of prostate that has led the bladder on to greater and greater compensation only to block suddenly is very likely to be one of mixed type with fibrous predominance located intra-urethrally, or one of large adenomatous type located either very high on the urethra or intracystically. As the former constitutes the larger class bringing about this change, and as it enucleates more easily without long drainage of the bladder, it does to this degree, favor the one stage operation in type. Gross pathologic classifications of benign conditions of the prostate (fibrous, mixed or adenomatous) have absolutely no individual constancy in the type of physiologic changes that they initiate or maintain. Similar mechanics of obstruction may be brought about by prostates of wide pathologic variance.

The two stage operation is favored in the face of marked decompensation of the wall of the bladder, as in this type drainage for relief is usually indicated, while the operative status of the patient is being determined. If this drainage is by urethral catheter, which is well borne in a decompensated wall, prostatic removal is indicated only after the infection associated with the catheter has subsided with continued suprapubic drainage.<sup>17</sup> These patients are easily recognized by the long history of dysuria and irritative symptoms at the time that they passed through their infection compensation, and later, decompensation to

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16. Rose, D. K.: *J. Missouri M. A.* **29**:10 (Jan.) 1932.

17. Thomas, G. J.; Exley, E. W., and O'Brien, W. A.: *J. Urol.* **15**:343, 1931.

subsequent greater dysuria. They usually show evidence of chronic infection and reduced renal function.

Any type of obstructing prostate may bring about a marked degree of decompensation if there is no interference by an exploring cystoscope of urethral catheter. When there has been such interference, however, the logical subsequent course is one of chronic infection with a reduced residual urine, the amount of the reduction indicating the amount of catheter compensation of the wall of the bladder and furnishing an index to the ratio between the expulsive force of the wall and the prostatic resistance.

Nearly complete obstruction, with a very high level of nonprotein nitrogen in the blood and a long history of dysuria, means a decompensated bladder wall. When there is no infection, no matter how complete the decompensation, return will be rapid, and the retention urethral catheter will be poorly borne. On this basis, it is best to institute suprapubic drainage without cystoscopic examination or cystogram, that is, without urethral trauma, leaving such procedures until renal function has improved. In certain bladders handled in this manner there is, at the ultimate time of closure of the suprapubic wound, a rise of temperature due to a bacterial invasion of the kidney, the seminal vesicles or the blood stream. This, in turn, is due to the high intracystic voiding pressure, that is, a long-contracted and infected bladder, and to an apparent lack of resistance to the infection, as the patient, at no time, has been subjected to infection plus increased intracystic pressure or to urethral foreign body. If, therefore, with the beginning of voiding through the urethra, the temperature rises, it is essential that means be used to decrease the infection of the bladder, and, at times, it may be necessary to reopen the suprapubic wound for a few days by passing a very small, wax bougie through the granulating wound in order that this intracystic pressure phase of the vicious circle may be broken.

As for minor operative procedures for the relief of prostatic obstruction, such as the various forms of prostatic punch, if the obstruction cannot be reduced below the level over which the expulsive force of the wall of the bladder will remain in easy, complete and permanent ascendancy, all are contraindicated on application of the foregoing principles.

Beaumont Medical Building.

# ETIOLOGY OF GALLSTONES

## I. CHEMICAL FACTORS AND THE RÔLE OF THE GALLBLADDER

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AND

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CHICAGO

The problem of cholesterol gallstone formation is essentially that of precipitation of cholesterol in the bile, because with remarkably few exceptions human gallstones are composed for the major part of cholesterol. This cholesterol may be of almost pure crystalline form or may be mixed with varying amounts of bile pigments or calcium, but the cholesterol-containing stones make up an enormous majority of all human gallstones, and according to Peel<sup>1</sup> the cholesterol content of mixed concrements averages at least 80 per cent. The only exceptions are the pigment stones or calcium carbonate stones. Such stones are quite rare in human beings, although they are common in animals. The entirely different composition of the two classes of stones, together with the fact that cholesterol stones are never found in animals, suggests the probability that they have an entirely different pathogenesis.

There are two problems to solve in the formation of cholesterol-containing gallstones: first, the means by which the cholesterol in the bile is precipitated and, second, the circumstances that are necessary to bring about sometimes typical stone formation with radial or concentric arrangement of crystals and at other times only single crystals. In the latter problem, the physical conditions of bile are of course important, and the time element is a great factor; we shall concern ourselves in this paper only with the first question. The consideration of the tiny pigment concretions studied by Naunyn,<sup>2</sup> Rovsing<sup>3</sup> and Rous<sup>4</sup>

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From the Department of Surgery of the University of Chicago. This work was done under a grant from the Douglas Smith Foundation for Medical Research.

1. Peel, A. A. F.: *Chemische Untersuchungen ueber Gallensteine und Galle*, Ztschr. f. physiol. Chem. **167**:250, 1927.

2. Naunyn, B.: *Cholelithiasis*, Leipzig, F. C. W. Vogel, 1892.

3. Rovsing, T.: *Pathogénie des calculs biliaires et indications opératoires*, Paris, Masson & Cie, 1925.

4. Rous, P.: *Physiological Factors in the Genesis of Gall Stones*, Proc. Inst. Med., Chicago **1**:33, 1928.

and of their acting as nuclei about which cholesterol precipitates seems to us to be entirely beside the point. Even if they are found at the center of some calculi, a fact that Aschoff<sup>5</sup> denied, the obviously decisive point is that neither they nor any other particulate matter will cause the crystallization of cholesterol out of normal bile, and an explanation must be sought of what factors influence the bile to bring about a supersaturation of cholesterol.

Cholesterol stone formation is also distinctly a human problem, as such concretions are never found in animals but are peculiar to man. In the gallbladder of the ox as well as in that of numerous experimental animals, the formation of stones is quite common, but these stones invariably are composed of bile pigment together with more or less calcium, and they never contain more than the faintest traces of cholesterol. Such stones have been produced by an enormous number of means which cannot be reviewed here, but the main factor in their formation seems to be stasis with inspissation of the bile due to the absorption of water. We know of but one paper in which the authors have claimed the formation of experimental cholesterol stones. Recently Wilkie<sup>6</sup> reported cholesterol stone formation in the rabbit by infection introduced either directly into the gallbladder or by intravenous injection. He gave no facts as to the amount of cholesterol and no results of analysis for cholesterol. This exception, therefore, seems doubtful, to say the least, and merely serves to emphasize the particular human specificity of cholesterol gallstone formation.

In the earlier studies of cholesterol metabolism attempts were made to link it with the formation of gallstones. However, the greatest stumbling block has been that, although by feeding or parenteral injection of cholesterol the cholesterol content of the blood may be lifted to a high level and deposits of cholesterol laid down in the aorta, suprarenals, etc., there has never been produced by this means a significant elevation of the biliary cholesterol, nor has it been shown by any one that the biliary cholesterol bears the slightest relation to the blood cholesterol. The literature on this subject was reviewed by McMaster.<sup>7</sup> While the total output of cholesterol may possibly be influenced by diet, the experiments of Naunyn,<sup>2</sup> Jankau,<sup>8</sup> Thomas<sup>9</sup> and Lichtwitz<sup>10</sup>

5. Aschoff, L.: Lectures on Pathology, New York, Paul B. Hoeber, Inc., 1924.

6. Wilkie, A. L.: The Bacteriology of Cholecystitis, Brit. J. Surg. **15**:450, 1928.

7. McMaster, P. D.: Studies on the Total Bile, J. Exper. Med. **40**:25, 1924.

8. Jankau, L.: Ueber Cholesterin und Kalkausscheidung mit der Galle, Arch. f. exper. Path. u. Pharmacol. **19**:237, 1892.

9. Thomas, quoted by McMaster (footnote 7).

10. Lichtwitz, L.: Ueber die Bildung der Harn und Gallensteine, Berlin, Julius Springer, 1914.



make it quite clear that the concentration of cholesterol in the bile remains the same even after feeding enormous amounts. McMaster<sup>7</sup> found a slight increase in the biliary cholesterol in dogs following diets high in cholesterol. The increase was not nearly as great, however, as that produced by starvation, and it represented only a very small fraction of the amount fed. For this reason all such attempts at the explanation of gallstones on the basis of hypercholesteremia have failed. These experiments also have led to numerous errors, as cholesterosis of the wall of the gallbladder is often observed after feeding experiments and is even found in many normal dogs. It has been assumed that this cholesterol is biliary in origin, when as a matter of fact further studies have shown that it is hematogenous in origin and that the biliary cholesterol remains normal.

At the outset of investigation, however, two points must be recognized. The first is the great difficulty of applying animal experiments to the human biliary system and the great likelihood of drawing false analogies, owing to fundamental differences in their behavior. In the bile of all animals that we have studied (ox, dog, rabbit, goat) the cholesterol content has been very low, indeed but a small fraction (from 10 to 20 per cent) of that of human bile. It is a common misapprehension that most of the cholesterol in the bowel is biliary in origin, whereas the overwhelming majority of it is excreted directly from the intestinal mucosa. Schoenheimer has shown that the colon,<sup>11</sup> jejunum and ileum<sup>12</sup> of dogs secrete very large amounts of sterol and that even the pancreatic juice<sup>13</sup> has about the same cholesterol content as bile. This will explain, therefore, the absence of cholesterol stones in animals, and no theory of human gallstone formation is valid unless it explains the absence of such a phenomenon in experimental animals.

The second important point is the insolubility of cholesterol in water which has been noted ever since its discovery. In the bile, however, it has been assumed, but never proved, that the substances that keep it in solution are the salts that occur in exceedingly high concentration in the bile (from 2 to 7 per cent). Solutions of bile salts have the power to dissolve surprisingly large amounts of this exceedingly insoluble substance. It is quite astonishing, therefore, that more work has not been done on this subject, as it so clearly must be related to the matter of gallstone formation. There are two kinds of bile acid known in human bile, cholic acid and desoxycholic acid, differing only in the number of hydroxyl groups (cholic acid contains three and desoxycholic

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11. Schoenheimer, R., and von Behring, H.: Ueber die Exkretion gasältigter Sterine, *Ztschr. f. physiol. Chem.* **192**:102, 1930.

12. Schoenheimer, R.: Data not yet published.

13. Dr. L. R. Dragstedt supplied large amounts of pancreatic juice for these studies.

acid two groups). A third bile acid, lithocholic acid, occurs in such a small amount that its presence can be neglected. As all bile acids are present in combined form with either glycocholl or taurine, four conjugated bile acids are important in human bile, glycocholic and taurocholic acid and glycodesoxycholic and taurodesoxycholic acid, all of which have more or less different physical and chemical properties. It has always been assumed that the simple uncombined acids are never found in bile. This matter will be discussed more fully in a later paper.

Thus far no quantitative method has been devised for the estimation of simple unconjugated bile acids. The combined bile acids can be accurately measured by the determination of the aminonitrogen in the bile by the Van Slyke<sup>14</sup> gas analysis method, as each molecule of either taurocholic or glycocholic acid contains one molecule of combined aminonitrogen (Schmidt and Dart<sup>15</sup>). A preliminary determination of aminonitrogen is made, as the bile contains small amounts of substances containing free amino groups. Then the bile is hydrolyzed at a pressure of 20 pounds in the autoclave for five hours in 8 per cent sodium potassium hydroxide, thus freeing the amino-acids in the combined bile acid. From the difference between the two readings one can readily calculate the bile acid content. On account of the large amount of substances present in the bile besides bile acids that react to the Pettenkofer tests (fatty acids, etc.), we do not feel that the quantitative Pettenkofer method is specific enough for use in the bile.

There are some difficulties in completely separating bile acids and cholesterol as they occur in human bile. This is evidenced by the fact that most commercial preparations of conjugated bile acids contain appreciable amounts of cholesterol in spite of the fact that attempts have been made to separate the two substances. The bile acids have the power to hold in solution numerous other ordinarily insoluble substances, especially those of a fatty nature. This can be shown crudely very simply by adding bile to milk. The latter immediately becomes clear and transparent owing to the dissolving of the fat droplets in the bile acid solvent, and fat droplets can no longer be seen under the microscope. Recently a similar rôle was ascribed by Walsh and Ivy<sup>16</sup> to the fatty acids that are present as soaps in the alkaline bile. To us this seems exceedingly doubtful. The amounts of fatty acids present in the bile are much too small to hold in solution as much cholesterol as is found in human bile. The bile acid content of the latter is quite

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14. Van Slyke, D. R.: The Quantitative Determination of Aliphatic Amino Groups, *J. Biol. Chem.* **12**:275, 1912.

15. Schmidt, L. W., and Dart, A. E.: The Estimation of Bile Acids in the Bile, *J. Biol. Chem.* **45**:145, 1920.

16. Walsh, E. L., and Ivy, A. C.: Observations on the Etiology of Gall Stones, *Ann. Int. Med.* **4**:134, 1930.

high and varies between 2 and 7 per cent, while the proportion of fatty acids is only a very small fraction of 1 per cent, an amount not nearly sufficient to dissolve any considerable percentage of the cholesterol. The determination of fatty acids in bile is extraordinarily difficult because these substances can be separated from the bile acids only with the greatest difficulty, as when acid bile is extracted with organic solvents, large amounts of bile acids as well as fatty acids are removed. Therefore, the standard methods used to determine fatty acids in blood or tissues are not applicable to the bile. Ivy determined the saponifiable material in bile in the expectation of arriving at an approximate estimation of the fatty acid content. It is obvious, therefore, that in his experiments the bile acids and fatty acids were not separated, and what he considered as saponifiable substances were really a mixture of fatty acids with overwhelming amounts of bile acids.

In our experiments it was attempted to investigate which of the various bile acids were responsible for the solubility of the cholesterol in the bile. The previous work of Wieland and Sorge<sup>17</sup> on the so-called choleinic acids seemed to give a key to the problem. Choleinic acid had formerly been considered to be a distinct bile acid, but these authors were able to show that it is a relatively loose chemical compound of desoxycholic acid with a mixture of fatty acids. These "addition compounds" of fatty acids and bile acids are comparatively stable substances. It is by this means that desoxycholic acid has the power to render soluble various ordinarily insoluble fatty acids. It was also shown that desoxycholic acid is able to make such addition compounds not only with the fatty acids but with numerous other substances ordinarily insoluble in water, in spite of the fact that they contain an insoluble fraction.

It can be seen from the results of the following experiments that cholesterol may be held in solution in the bile in a similar addition compound not only with desoxycholic acid but with all the other bile acids as well.

Theoretically, if the cholesterol in the bile is held in combination with the bile salts, precipitation of the cholesterol should occur if the bile salts are removed from the solution by any means. Throughout our experiments this was always actually the case. Part of the bile acids are insoluble in water, and if bile is acidified the soluble salts of the bile acids are changed into the insoluble acids which are precipitated. Such a precipitate always contains large amounts of cholesterol.

The following series of experiments in which the various bile acids are precipitated in rotation by specific substances indicates that each of

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17. Wieland, H., and Sorge, H.: Untersuchungen ueber die Gallensauren. *Ztschr. f. physiol. Chem.* 97:1, 1916.

the fractions carries with it part of the cholesterol. Human bile, after deproteinization, was treated with iron chloride. This precipitates most of the glycocholic acid and glycodesoxycholic and taurodesoxycholic acid. Lead acetate may also be used for this purpose. The precipitate was treated with sodium carbonate to reform the soluble sodium salts. The salts were then dissolved in alcohol, and digitonin was added. There was a typical precipitate of the insoluble cholesterol digitonid. However, after the removal of the heavy metal precipitate, the bile still contains some cholesterol while held in solution by the remaining bile acids which are not precipitated by the heavy metals. Most of these remaining bile acids, mainly taurocholic acid, may be salted out of the solution by saturation with sodium chloride or ammonium sulphate. This fraction of taurocholic acid, if redissolved in alcohol, may be demonstrated to contain cholesterol also by the digitonin method. The difficulties of isolating the entire series of bile acids quantitatively from human bile are, with the present knowledge, practically insuperable, and considerable amounts of them are lost in purification by recrystallization or other chemical means. However, it was finally possible to secure fractions that consisted practically of a single kind of bile acid and a lesser amount of cholesterol. The cholesterol content of these complexes was from 6 to 8 per cent, and in spite of this high content of insoluble cholesterol they would all dissolve readily in water, giving perfectly clear solutions. The results of these experiments indicate that not only the salts of the desoxycholic acids but also those of the other bile acids are able to form with cholesterol complexes similar to the addition compounds of Wieland and Sorge.<sup>16</sup>

In order to study the properties of these complexes more accurately, attempts at synthetic preparation of the various complexes were carried out in the following manner: The pure sodium salt of the bile acid was heated in alcohol solution with an excess of cholesterol, and the alcohol was then completely evaporated off in a water bath. The residue was boiled for several hours with twenty volumes of water under a reflex condenser, and the excess cholesterol was thus gathered in large masses and could easily be filtered off. The remaining clear, watery solution was then evaporated to dryness.<sup>18</sup> These further purified substances are very easily soluble in water, giving a perfectly clear solution, and correspond in all their physical and chemical properties to the complexes that had been isolated from the bile. Such complexes of cholesterol and bile salts are all soluble in water, but are all insoluble in the acid form, the only exception being taurocholic acid, which is

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18. The further purification of these substances was carried out in different ways according to the type of bile acids used. These purely chemical data are being reported elsewhere.

soluble in acid as well as in alkali. This exception in the case of taurocholic acid has considerable clinical interest, as it is theoretically possible at least that by this means the cholesterol in the bile would be protected in its solubility against changes in the acidity of the bile, and in view of the great excess of bile acids, taurocholic acid alone would have the power in most cases to hold the cholesterol in solution.

It appears, then, that the complexes isolated from the bile and those prepared synthetically are identical. The stability of the union in this complex is in most cases loose, but the desoxycholic acid complex is considerably more firmly bound together. The complexes derived from glycocholic and cholic acids are considerably less stable than the others, and although they are stable in solution, in the dried form they tend to separate into their components. The addition of organic solvent permanently breaks up the complex, at least in part, almost certainly owing to the fact that these solvents themselves displace the cholesterol and enter into similar complexes with the bile acids. Xylene and ether for example, both have this property. As was mentioned, digitonin will precipitate the cholesterol from a solution of the complex.

One of the most interesting studies made, and one that has an obvious clinical application, is the experiments with a dialyzing membrane. Bile acids are easily dialyzable, and experiments were made to see if, as they pass through a membrane, they would carry the cholesterol in solution with them. Solutions of various complexes, 5 per cent in strength, were dialyzed in a parchment membrane against water. After from four to twenty-four hours, it was noted that the solution in the membrane, which had been perfectly clear, had become cloudy. Microscopic and chemical tests showed that this turbidity was due to the precipitate of amorphous or crystallized cholesterol, and that the fluid outside the membrane contained bile acids but no cholesterol. It was obvious that the bile acids, by leaving the membrane, had so reduced the bile acid content within, that there was not sufficient solvent left to hold the cholesterol in solution and it was therefore precipitated. In studying our pure synthetically prepared complexes in this manner, this same phenomenon was observed throughout the series, with the exception of desoxycholic acid and taurocholic acid. These groups appeared to have the power to make a firmer union with the cholesterol, and separation by dialysis could not take place. This phenomenon occurs not only in the synthetically prepared products, but can be demonstrated in human gallbladder bile very simply; if the latter is dialyzed against water, the bile soon becomes turbid with cholesterol. and large amounts of bile acids can be found outside the membrane. With bile acid fractions from the dog or ox this phenomenon is much less marked; the dialysis must be prolonged until the extraction of

bile acids is almost complete, and even then but a very slight turbidity will appear because of the minute amounts of cholesterol in these substances.

Similar experiments for other purposes have been carried on by Verzar.<sup>19</sup> He brought cholesterol into aqueous solution by pouring a 10 per cent solution of cholesterol into a 5 per cent aqueous solution of bile salts. This solution, which still contained alcohol, was dialyzed against a 5 per cent solution of the same bile salt without cholesterol (and alcohol?). After a certain time, using the very sensitive Salkowski reaction, he found cholesterol outside the membrane and believed that the bile acids had made the cholesterol dialyzable. As we did not believe his conclusions, we repeated the experiment, using not a solution containing alcohol, as Verzar did, but the complex of sodium glycocholate with cholesterol which, as has been mentioned, is very easily water-soluble. Outside the membrane was a 5 per cent solution of sodium glycocholate, which was previously purified, because most preparations of this substance on the market contain more or less cholesterol. We could not find the smallest traces of cholesterol outside the membrane after dialysis for twenty-four and forty-eight hours. The results of Verzar can be explained by the fact that he dialyzed alcoholic solutions against watery solutions. Also he did not mention whether the sodium glycocholate outside the membrane was purified to remove the last traces of cholesterol which could have given the Salkowski reaction.

The problem as to whether these complexes isolated from the bile that were synthetically prepared are actual addition compounds or whether they represent simply a phenomenon of common solubility cannot be answered as yet, as further work is necessary involving crystallographic studies, molecular weights, optical rotation studies, etc. It is certain, however, that at least the desoxycholic acid-cholesterol complex appears to be a definite chemical compound. In the human bile, therefore, part of the cholesterol is firmly bound and another part is more loosely bound. The investigation of the properties of these individual substances is being further continued. It is obvious from the data presented that the maintenance of the cholesterol in solution in the bile is dependent on its bile acid content. As soon as the bile acid content falls below a certain level the cholesterol is precipitated, with the obvious implication of possible formation of gallstones. From our experiments in the preparation of synthetic addition compounds, as well as from actual studies of the bile itself, it appears that this critical level is reached when the bile salt-cholesterol ratio reaches about the level of 13, and if it falls below this level precipitation will occur. In human

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19. Verzar, F., and Kuthy, A.: *Die physiologische Bedeutung der Hydrotropie*, *Biochem. Ztschr.* **225**:267, 1930.

bile the average bile salt-cholesterol ratio is 20:30, and it is obvious that this is dangerously near the critical point and that a relatively slight disturbance will bring about precipitation.

In the animals thus far studied (goats, rabbits, cattle and dogs), while the bile salt content approximates that of human bile, the cholesterol content is very small, so that the ratio is much higher than in human bile, generally about 100. It is clear, therefore, that in animals there is a wide range in which variations in the ratio may occur without coming near the danger point, and one can see why cholesterol gallstones never occur in animals nor can be produced experimentally, while in the human being gallstones are predominantly made of cholesterol.

After recognizing the importance of the bile salt-cholesterol ratio for the formation of gallstones, one can theoretically see two possibilities of its application to clinical disease, the first being a differential absorption of the two substances by the mucosa of the gallbladder in the process of concentrating the bile, and the second, the excretion by the liver of bile containing so low a proportion of bile salts that they could not hold the cholesterol in solution. The experiments reported in this paper were undertaken in order to study the rôle of the absorptive mechanism in the gallbladder as a factor in changing the bile salt-cholesterol ratio.

#### EXPERIMENTATION

The first step was to determine the action of the normal gallbladder in its concentration of the bile. This was done in the following manner. It was assumed that thirty-six hours' starvation was the maximum that could occur under physiologic conditions. Also it is well known from the work of other students that the maximum or nearly maximum concentration of the bile occurred in about that period. Therefore, the animals were starved for that thirty-six hours so that no gallbladder contractions would occur, and at the end of that time they were anesthetized with barbital, the abdomen was opened, the cystic duct was clamped at once to prevent further escape of bile, and the common duct was cannulized. After sufficient liver bile had been secured for analysis, the animals were killed by electrocution and the gallbladder bile and concurrently secreted liver bile were analyzed. This was assumed to show the normal action of the gallbladder mucosa.

The results of these analyses are shown in table 1. The concentration of the bile in the gallbladder as measured by us in this as well as in numerous other experiments using the bile salts and cholesterol as indexes is from three to ten times that of the liver bile, most of the figures lying distinctly in the lower half of the range. The higher values are generally due to the concentration by the gallbladder of

rather dilute bile which is often concentrated to the same levels in the gallbladder as are the thicker biles. There seems to be a rough limit beyond which the normal gallbladder in dogs does not go, even if it starts with very thick bile. This is represented by the level of about 25 per cent total solids. When total solids are used as an index of the concentrating power of the gallbladder, it must of course be remembered that while water and salts are absorbed, considerable amounts of protein are excreted, mucus by the normal gallbladder and serum proteins as well by the inflamed viscus. We have not used bilirubin as an index of concentration in any of our work on account of the extremely fluctuant results obtained under certain conditions. For instance, Drury<sup>20</sup> once found a concentration of fifty-eight times the bilirubin in the liver, and on several other occasions almost equally high figures.

TABLE 1.—*Concentration of Bile by Normal Gallbladder. Simultaneous Estimation of Gallbladder and Liver Bile in Starving Dogs*

Dog	Total Solids		Calcium		Cholesterol		Bile Salts		Ratio Bile Salts to Cholesterol	
	Gall-bladder Bile	Liver Bile	Gall-bladder Bile	Liver Bile	Gall-bladder Bile	Liver Bile	Gall-bladder Bile	Liver Bile	Gall-bladder Bile	Liver Bile
654.....	25.88	12.19	54.6	14.3	74	20	5,697	1,935	80	96
671.....	24.15	4.3	52.7	10.0	65	16	5,885	747	90	48
677.....	25.27	5.7	66.4	16.1	90	18	6,385	1,322	72	76
696.....	23.10	7.1	56.6	15.8	60	15	5,515	1,657	92	116
704.....	23.44	4.97	56.0	11.3	54	21	4,562	407	92	20
Average.....	22.04	6.4	57.2	13.5	68	18	5,610	1,214	85	71
Concentration....	3.4 times		4.2 times		3.7 times		4.6 times			

This is obviously an impossible figure, as the biliary constituents are not soluble to anywhere near such a degree. The method of estimation of bilirubin is colorimetric, and, as he suggested, the marked acidification of the bile in the gallbladder may cause changes in the pigments that render the colorimetric estimation inaccurate.

However, whatever index is used, it can readily be seen that there is no lowering in the bile salt-cholesterol ratio by the normal gallbladder (table 1). While the gallbladder bile is from three to four times as concentrated as the liver bile, the figures show that in relation to the cholesterol content the bile salt content certainly does not fall. The average concentration of the cholesterol is 3.7 times that in the liver, while the average concentration of bile salts is 4.6 times. The average bile salt-cholesterol ratio is 71 in the liver bile and 85 in the gallbladder

20. Drury, D. R.: Studies on Total Bile: VIII. Conditions Influencing Calcium Content of Bile, *J. Exper. Med.* **40**:797, 1924. Drury, D. R.; McMaster, P. D., and Rous, P.: Observations on Some Causes of Gall Stone Formation, *ibid.* **39**:403, 1924.



bile. These figures in our opinion lie well within the margin of experimental error, which is considerable in the colorimetric cholesterol estimations. On account of the small size of many of the samples, the more accurate digitonin method could not be used. One is not warranted, therefore, in assuming that there is any differential absorption of the two substances by the normal gallbladder. This agrees with the commonly accepted hypothesis that the normal gallbladder absorbs only water and inorganic salts.

The action of the abnormal gallbladder was studied in a different manner. A series of dogs were anesthetized, the abdomen was opened, and the cystic duct was tied, care being taken not to injure the cystic artery. The gallbladder was then aspirated with a large needle and half of the contents was saved for analysis and the other half reinjected into the gallbladder and left there for twenty-four hours, at the end of which time the dog was killed and the two specimens of bile were compared.

In a previous paper<sup>21</sup> it was shown that the gallbladders of dogs treated in this manner promptly underwent severe degenerative changes, owing to infection arising in the stagnant and traumatized gallbladder. The bile, which is sterile in such animals, promptly becomes infected by a great number of organisms which can be demonstrated either by culture or smear. Microscopic section of the wall of the gallbladder shows that there is a marked onset of a moderately severe inflammatory process. As a matter of fact, microscopic section is hardly necessary, because the majority of the gallbladders treated in this manner appear whitish and grossly thickened, and there are more or less denudation of the mucosa and ulceration. Part of the dogs in this series were also subjected to the additional trauma of curettement of the inside of the gallbladder through a small hole. The holes in the gallbladder, whether for the large needle or for the curet, were closed by ligation, and the thickening and inflammation in the region of the ligature were especially marked. There can be no doubt, therefore, that we were dealing in this series of experiments not only with the factor of the stasis of the bile but with the factor of an obstructive pathologic condition in the gallbladder. In fact, it is very difficult, as was noted in our previous publication, to produce stasis of any sort without prompt onset of sepsis.

The results of the analysis of the action of the abnormal gallbladder are shown in table 2 and afford a striking proof of the differential absorption of the cholesterol and bile acids by such a viscus. Throughout the series there was a constant rise in the cholesterol content, accompanied by an equally constant fall in the bile acids. The average was

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21. Andrews, E., and Hrdina, L.: Hepatogenous Cholecystitis. *Proc. Soc. Exper. Biol. & Med.* **28**:116, 1930.

a 28 per cent fall in the bile acids and a 29 per cent rise in the cholesterol, so that in the entire series the bile acid-cholesterol ratio of the controls was 97 and in the experimental series only 59. A study of the total solids in the bile shows that during the period of the experiment there was an average concentration of the bile of 10 per cent, so that these figures become still more striking, there being about a 40 per cent change in the bile acid-cholesterol ratio. The apparent rise in the cholesterol content in these series might be thought to be indicative of an excretion of cholesterol by the gallbladder, and the results of these

TABLE 2.—*Concentration of Bile by the Abnormal Gallbladder. The Cystic Duct was Tied, a Specimen was Aspirated from the Gallbladder, the Needle Hole was Ligated, and Twenty-Four Hours Later the Animals Were Sacrificed and a Second Chemical Analysis of the Gallbladder Bile was Made*

Dog	Total Solids		Bile Acids		Cholesterol, Mg. per 100 Cc.		Change, per Cent		Ratio Bile Salts to Cholesterol	
	Nor-mal	Experi-mental	Nor-mal	Experi-mental	Nor-mal	Experi-mental	Bile Salts	Choles-terol	Nor-mal	Experi-mental
859	.....	.....	6,040	5,327	54	58	—12	+ 6	112	92
885	.....	.....	4,600	1,880	48	58	—59	+20	96	32
889	.....	.....	6,010	3,910	45	70	—35	+49	131	55
892	.....	.....	4,862	4,647	40	47	— 5	+17	121	99
955	0.2320	0.2129	5,272	3,552	38	45	—33	+18	139	79
960	0.2130	0.3023	5,312	4,843	55	67	— 9	+23	97	72
961	0.2371	0.2516	5,572	3,260	56	77	—42	+37	99	43
962	0.2086	0.2662	5,705	2,512	49	71	—56	+42	117	35
923*	0.2245	0.3040	3,222	2,735	80	54	—15	—33	30	51
966	0.2930	0.2611	4,962	4,747	52	78	— 5	+50	94	61
968	0.2267	0.2539	4,615	3,755	50	54	—19	+ 9	92	69
18	0.1808	0.2514	5,827	5,765	50	64	— 3	+26	116	90
19	0.2256	0.1690	4,575	2,027	55	57	—69	+ 2	83	36
881†	0.2307	0.2567	3,352	.....	66	121	....	+83	51	..
883†	0.2050	0.2575	4,245	1,930	50	94	—55	+85	105	20
887†	0.2362	0.2791	4,825	4,595	68	79	— 5	+16	71	58
Aver.	0.2267	0.2554	.....	.....	..	..	—28	+29	97	59

\* Pregnant dog. No explanation can be offered of the curious fact that this is the only negative change in the entire series.

† Gallbladder curetted.

experiments are typical of some work reported by other observers and interpreted in this manner. However, when one realizes the small amount of cholesterol in the bile of a dog (from 10 to 20 mg. per hundred cubic centimeters) and the high cholesterol content of the blood of the dog (from 200 to 300 mg. per hundred cubic centimeters), it is obvious that the results secured are no proof whatsoever of the secretion of cholesterol by the gallbladder wall, as the leakage of only two drops of blood or serum would more than account for the rise in the cholesterol. In the presence of frank infection, such as occurs in these cases, there is always a rise in the leukocytes in the bile, which will autolyze, and as leukocytes contain nearly 0.5 per cent of cholesterol,

the rise could be accounted for easily on this basis. It is obvious, however, that the diseased gallbladder acts exactly as the dialyzing membrane described in the earlier part of the paper, and that through its inflamed or denuded wall the bile acids will pass and the cholesterol will remain behind. It is clear that if this process continues very long in man, in whom the bile acid-cholesterol ratio is from 20 to 30, instead of about 100 as in the dog, it is possible to reach the critical point of precipitation of cholesterol within twenty-four hours after the reaction produced at the same rate as in the dog's bladder, and that this phenomenon is ample to account for the formation of cholesterol gallstones. If the bile salt-cholesterol ratio is at the level of 20 in the normal man and can be lowered 40 per cent in twenty-four hours, as occurs in the

TABLE 3.—*Human Gallbladder Bile in Cholelithiasis* \*

Case	Cholesterol	Bile Salts	Ratio Bile Salts to Cholesterol
34963.....	69	1,130	17.0
32259.....	78	175	2.2
3971.....	138	1,302	8.8
33293.....	114†	0	0
35567.....	138	272	2.0
34904.....	188	1,310	7.0
35861.....	96	735	7.6
37847.....	282†	0	0
12869.....	360	45	0.12
38517.....	38	622	17.0
38764.....	15†	0	0
37714.....	128	344	2.6
Average.....	136	497	3.7
Mixed bladder bile from 30 postmortem cases of stones.....	400	247	0.6

\* The bile salt-cholesterol ratio in normal human gallbladders is 20:40.

† Bile contained cholesterol crystals.

dog's gallbladder under relatively slight conditions of infection, one would be exactly at the critical point of precipitation, about 13.

If our theory of gallstone formation is true, one would expect to find in the human stone-containing gallbladders a much lower bile acid-cholesterol ratio than in the normal gallbladder. While the actual percentage of cholesterol itself is not important, the presence of sufficient bile salts to hold it in solution is the crucial point. Previous studies of this sort have been made by Newman <sup>22</sup> who analyzed the gallbladder bile in a long series of autopsies on bladders with and without stones. He reported that the cases with cholesterol-containing stones or cholesterol crystals showed a higher bile acid-cholesterol ratio than was found in the normal gallbladders or in those containing pigment or calcium

22. Neuman, C. E.: Beiträge zum Studium der Gallenniederschlags und Gallensteinsbildung, Beitr. z. path. Anat. u. z. allg. Path. 86:187, 1931.

stones. We have analyzed the mixed gallbladder bile in a postmortem series of 30 stone-containing gallbladders.<sup>23</sup> Our observations in the postmortem cases confirmed those of Newman; the cholesterol content was 400 and the bile salt content 247 mg. per hundred cubic centimeters, the former figure being about normal and the latter only about one twentieth of the normal gallbladder content of bile acid. The average bile salt-cholesterol ratio in our series was 0.6, which offers a very striking contrast to the normal figures of from 20 to 30.

We have extended these studies to include fresh operative material. The gallbladder contents in twelve cases of cholesterol stones removed at operation were studied. As can be seen in table 3, the cholesterol content of this bile was quite within the normal range, but the bile salt was only about 10 per cent of the amount to be expected in the normal human gallbladder, while the average bile salt-cholesterol ratio was 3.7, representing a marked lowering of the normal bile salts and only a small fraction of the usual content. It is very difficult to get normal figures as to the normal gallbladder content in the human being as most of our analyses have been from postmortem material. However, the figures generally given are from 6 to 8 per cent of bile acids. Hammersten analyzed the bile in two cases of accidental death, and his analysis shows a bile salt-cholesterol ratio of about 40, the bile acid content being 8.2 and 8.7, respectively. These figures agree fairly well with the results of the series of analyses of normal human gallbladder bile made by Neuman. It is further interesting to note that in our series there were three cases of complete prolonged obstruction of the cystic duct, as shown by failure to visualize the gallbladder over a long period of time. In all of these cases there was a total absence of bile acid in the gallbladder bile, and in each case the cholesterol in the bile was precipitated and was in the form of a crystalline suspension. This may be regarded as a further proof of differential absorption of the biliary constituents in the abnormal gallbladder.

#### SUMMARY

1. The cholesterol is held in solution in the bile in a series of loose and firm chemical complexes with the bile salts.
2. Most of these complexes may be broken up by relatively slight influences, as for instance, by dialysis.
3. If the bile salts are removed from these complexes or from bile by any means, cholesterol is precipitated.
4. There is no differential absorption of cholesterol and bile salts by the normal gallbladder.

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23. This material was kindly furnished to us by Dr. R. H. Jaffe from the Cook County Hospital, Chicago.

5. The infected gallbladder absorbs bile salts rapidly, but cholesterol very slowly, if at all.

6. Therefore, the bile salt-cholesterol ratio is of supreme importance in the precipitation of cholesterol from the bile.

7. The low bile acid content of the cholesterol stone-containing gallbladder bile from autopsy material, as reported by Neuman, is confirmed and extended to fresh operating room material.

#### CONCLUSION

Cholesterol precipitation from the bile, with its implication of gallstone formation, is caused by a lowering of the bile salt content of the bile.<sup>24</sup>

NOTE.—Since this paper was written attention has been called to an article of Elman and Graham (The Pathogenesis of the "Strawberry" Gallbladder [Cholesterosis of the Gallbladder], *ARCH. SURG.* **24**:14 [Jan.] 1932), in which our work was quoted in support of the theory that cholesterol is excreted by the mucosa of the gallbladder. This confusion was probably caused by the fact that in the preliminary report of this work our tables were omitted, but it is clear from tables 1 and 2 that although the cholesterol may be in a higher concentration, this fact is nullified by the corresponding inspissation of the bile as evidenced by total solids. We do not believe that the gallbladder mucosal secretion is a factor in gallstone formation; this feature has been discussed in a subsequent article (Andrews, E.; Hrdina, L., and Dostal, L. E.: Studies on the Etiology of Gallstones: II. Analysis of Duct Bile from Diseased Livers, *ARCH. SURG.*, to be published).

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24. It has been found that the cholesterol in pancreatic juice is removed by the Berkefeld filter and is therefore presumably not in the form of a solution.

# FORTY-EIGHTH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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(Concluded from page 614)

## MISCELLANEOUS

*Osteosclerosis Fragilitas*.—Windholz<sup>20</sup> reported a case of generalized osteosclerosis fragilitas, marble-bone disease, in a 11 month old child. The bones were particularly rich in calcium, and no marrow cavity was demonstrable. All of the bones were equally involved. Banded transverse shadows were present in the metaphyseal regions. No fractures were demonstrable. There was periosteal new bone formation. A bilateral optic atrophy was present. There was a family history of inbreeding. The author mentioned that in the other cases of marble-bone disease reported in the literature consanguinity was a frequent finding. Fractures were common, presumably because of the decrease in the relative proportion of connective tissue in the bone, hence the name fragilitas. Atrophy of the optic nerve usually occurred due to the narrowing of the foramen of the orbit. Periosteal changes comparable in appearance were observed in some leukemias and ergosterol poisoning. Alterations in the blood picture were frequently observed. No etiology was known, although a disturbance in the glands of internal secretion had been suggested.

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20. Windholz, F.: Ztschr. f. Kinderh. 51:708, 1931.

*Callus Formation of the Tibia Without Fracture.*—Ollonqvist<sup>21</sup> described a new disease of the inner aspect of the tibia. It consisted of a localized osteoperiostitis of the inner aspect of the tibial shaft, demonstrable roentgenologically and histologically. In all, sixty cases were seen, mostly in young recruits of about 20 years of age. Gradually, on assuming military service, local pain appeared. Early roentgenograms were negative. A deposit of smooth callus began to appear slowly, which after three or four months was easily visible. In from two to four months more, symptoms had disappeared. The author believed that the lesion was due to the traumas of impact, somewhat as in the case of "March-foot." Bacteriologically studied, the excised specimens were sterile. There was no syphilis. Ten excisions were performed.

[ED. NOTE.—This is an interesting entity. The causative mechanism is not yet clear.]

Pellegrini-Stieda's disease, or calcification of the internal lateral ligament of the knee, was believed by Rouillard and Bousser<sup>22</sup> to be a clinical entity. It occurred in adults, usually males, following trauma. Injury might be slight but more often was severe, either direct or indirect trauma. At first the symptoms were those of any knee injury. There was then a period of improvement but never complete recovery. After weeks or months, disturbance of function and pain increased until they reached a point at which they were stationary. Motion was limited. There was tenderness over the internal condyle and often the condyle appeared hypertrophied. Roentgenograms were essential for diagnosis. They showed a shadow of bony density along the lateral border of the internal condyle, either continuous or composed of a string of separate shadows. They usually began at the level of the knee joint. Early cases showed the ossification separated from the condyle and late cases showed it apparently united to the condyle. In the latter group of cases roentgen examination did not disclose whether the condition was a fragment of the condyle or a calcification of the internal lateral ligament. Histologic examination, however, showed the latter to be the case. The authors described a case which suggested that a single trauma might not be necessary to cause this condition but that it might be due to repeated small strains due to faulty weight-bearing and to an associated hypertrophic arthritis.

[ED. NOTE.—Our understanding of Pellegrini-Stieda's disease is different from that of the authors. In this disease as previously described the calcification has been at the attachment of the adductor

21. Ollonqvist, L. J.: *Arch. f. klin. Chir.* **166**:412, 1931.

22. Rouillard, J., and Bousser, J.: *Bull. et mém. Soc. méd. d. hôp. de Paris* **47**:1739 (Nov. 23) 1931.

magnus and not at the internal lateral ligament (see Forty-Sixth Report of Progress). It seems that a distinction should be made between these two conditions.]

*Callus Formation and Endocrine Influence.*—In discussing his experience in increasing callus formation with thymus and hypophysis extracts. Bergmann<sup>23</sup> said he believed that there was no specific stimulant even though both of these substances increased the amount of callus formed. What was needed was not a substance to increase the amount of callus but a product which would cause the deposition of a small but rapidly ossifying callus. Such an aid had not as yet been discovered.

*Sequestrums in the Femoral Head.*—Bergmann<sup>24</sup> presented examples of various pathologic entities which had in each instance led to the same result—the formation of a wedge-shaped area of devitalized bone in the head of the femur. In tuberculosis these sequestrums remained attached to the surrounding viable bone and were separated with difficulty. In acute pyogenic inflammatory lesions the sequestrums were rapidly demarcated and loosened. In the aseptic necrosis following traumatism to the hip joint from traumatic dislocation or reduction of congenitally dislocated hips, the sequestrums remained attached to their sites for the most part. They might, however, be freed by trauma later, and become joint mice. Areas of aseptic necrosis appeared in arthritis deformans as well as in osteochondritis dissecans.

*Various Forms of Meniscus Cysts.*—Mandl<sup>25</sup> pointed out that cysts of the meniscus might be of two sorts. The parameniscal cysts arose from the lateral edge of the cartilage in the region of the capsule where its blood supply was best, and extended from the outer layers of the meniscus into the adjacent capsule. Removal of the meniscus and adjacent involved capsule was advisable. The intrameniscal cyst was quite different. Clinically, it was differentiated from ruptured meniscus only with great difficulty. The cartilage on inspection at operation was generally stained and was the color of ivory. A break was often apparent, and no cyst was visible. However, microscopic examination revealed that there was a cyst which had ruptured and smaller cysts lined with degenerated stroma but without endothelial lining might be demonstrated. In two of twenty-three cases of pathologic menisci, such cysts were found. Removal of the cartilage itself was quite sufficient.

*Gangrene of the Extremities in Diabetic Patients.*—Escudero and Schultz Ortiz<sup>26</sup> reported fifty-eight cases of gangrene in the extremities

23. Bergmann, E.: Deutsche Ztschr. f. Chir. **233**:302, 1931.

24. Bergmann, E.: Deutsche Ztschr. f. Chir. **233**:252, 1931.

25. Mandl, F.: Deutsche Ztschr. f. Chir. **233**:262, 1931.

26. Escudero, P., and Schultz Ortiz, G.: Semana med. **2**:1914 (Dec. 24) 1931.



of diabetic patients treated in the Hospital Rawson, Buenos Aires; fifty-two were in the lower extremity and six in the upper extremity. The prognosis depended on the evolution and type of gangrene. The best treatment was local prophylaxis combined with medical treatment of the diabetes. In six cases of gangrene cure was obtained by conservative therapy: medical care combined with local physical therapy, rest, baths and exercises. Thirty-five amputations were performed, all in gravely ill patients. Fourteen of them recovered. The authors felt that the site of election in amputation in the lower extremity was the upper third of the lower portion of the leg and the lower third of the thigh since the best blood supply was obtained in these areas.

*Method of Determining the Angle of Torsion of the Neck of the Femur.*—Rogers<sup>27</sup> described a simple method whereby the torsion (anteversion) of the femoral neck might be determined by fluoroscopy. The patient was laid face down on the fluoroscopic table and the tube centered under the affected hip. The knee was then flexed to a right angle and the thigh slowly rotated outward until the femoral head lay directly in line with the shaft. In coxa valga the head appeared above the trochanter, and in coxa vara it was superimposed on the trochanter but as long as it was in line with the shaft its position upward or downward made no difference. The angle that the lower part of the leg, when flexed, made with the table then gave the angle of torsion of the femoral neck. The author showed by a simple diagram how this conclusion was arrived at.

[ED. NOTE.—The x-rays and fluoroscope are diagnostic aids which are seldom used to their fullest advantage. Any simple elaboration of the usual technic of anteroposterior and lateral and stereoscopic views is worth emphasizing, and an exact method of measuring torsion of the femoral neck should be useful, particularly in dealing with cases of congenital dislocation of the hip.]

*Significance of Fat Embolism.*—The incidence of fat embolism in subjects coming to medicolegal autopsy was discussed by Vance.<sup>28</sup> An overwhelming percentage of the cases showing fat embolism in the lungs and kidney (the two tissues examined) had received one or more fractures. The author believed that this substantiated the mechanistic theory of fat embolism as postulated by Gauss,<sup>29</sup> and that the true etiologic factor in fat embolism was trauma to fatty tissue. Shock he

27. Rogers, S. P.: J. Bone & Joint Surg. **13**:821 (Oct.) 1931.

28. Vance, B. M.: The Significance of Fat Embolism, Arch. Surg. **23**:426 (Sept.) 1931.

29. Gauss, H.: The Pathology of Fat Embolism, Arch. Surg. **9**:592 (Nov.) 1924.

thought was a condition totally distinct from fat embolism. A large bibliography was given and the present chemical and pathologic findings summarized.

[ED. NOTE.—The forced introduction of liberated fat into patent blood vessels is the most generally accepted explanation of fat embolism today. The relation between shock and fat embolism is not clearly understood, however, and some recent experimental work would tend to show that perhaps fat embolism is one of the phenomena of shock and not the cause of it.<sup>30</sup>]

#### SURGERY OF BONES, JOINTS AND TENDONS

*Incision for Exposure of the Elbow Joint.*—Campbell<sup>31</sup> described a new operative approach to the elbow joint, but attributed priority to Mr. W. H. L. Molesworth of Folkestone, England. He claimed that an excellent exposure was obtained and that the approach was less traumatic than others commonly used. Through a median longitudinal incision, after isolation and retraction of the ulnar nerve, the medial epicondyle of the humerus was detached and retracted with its muscular attachments. The joint capsule was then incised and the periosteum with the anterior and posterior capsule may be stripped from the humerus as far as required for exposure. This gave free access to the joint.

*Operative Cure of Hallux Valgus and Bunions.*—Kleinberg<sup>32</sup> emphasized the importance of adduction of the first metatarsal (metatarsus primus varus) in the causation of hallux valgus. He resected the metatarsocuneiform joint, thus correcting the varus of the metatarsal, and removed the bursa and exostosis at the metatarsophalangeal joint through a second incision. Eight persons so treated had done well.

#### FRACTURES AND DISLOCATIONS

*Treatment of Compound Fractures in Civil Practice.*—Creysse and Armanet<sup>33</sup> reviewed forty cases of compound fracture of the lower portion of the leg. The fractures were divided into three groups and the following conclusions as to treatment were drawn: Group 1 consisted of fractures with small puncture wounds presumably made from within out. The authors found that the general impression that there was little danger of infection was unfortunately not true. If there was any doubt, it was best to do a wide débridement. Some of the indications for débridement were oozing of old blood from the wound,

30. Lehman, E. P., and McNatin, R. F.: Fat Embolism, Arch. Surg. **17**:179 (Aug.) 1928.

31. Campbell, W. C.: Am. J. Surg. **15**:65 (Jan.) 1932.

32. Kleinberg, S.: Am. J. Surg. **15**:75 (Jan.) 1932.

33. Creysse, J., and Armanet, M.: Rev. de chir. **50**:582 (Oct.) 1931.

edema of the soft parts, absence of diminution of dorsalis pedis pulse. When débridement was not done the puncture wound was never sewed up. Group 2 was composed of fractures with large wounds and injury to the soft part. Amputation was often the only course to pursue. The surgeon should not hesitate to amputate. Amputation permitted hemostasis; it stopped the absorption of toxins from injured tissues and also eliminated the painful and deformed legs which had often been saved with much difficulty only to need a secondary amputation later. Group 3 consisted of fractures intermediate between groups 1 and 2. In this group were those with bone ends protruding from the wound. The bone was considered infected and was thoroughly cleaned. A wide débridement of soft parts was done. The wounds were left wide open and the temptation to plate the bone ends was resisted. Secondary suture and secondary plating were rarely necessary. This group also included those without protrusion of bone ends. Treatment was conservative. Fixation was used only when position could not be maintained with traction or plaster and then in the simplest way possible.

*Rare Dislocations of the Foot.*—Skrivanek<sup>34</sup> discussed lucidly the mechanism of dislocations of the subastragalar and midtarsal joints. He emphasized the necessity of roentgenograms in two places. Reduction was essential. Subastragalar dislocations could be handled by closed manipulation under general or local anesthesia if seen early enough. However, isolated talonavicular dislocations, with rare exceptions, required open reduction even if seen early. Ultimate function depended in large measure on the amount of initial and surgical trauma. Often, however, an anatomically poor result would function well.

*Paravertebral Intramediastinal Hematoma in Fracture of the Vertebra.*—Eiselsberg and Gold<sup>35</sup> called attention to the interesting shadows of hematomas in vertebral fracture which could be seen during the first week. These were found in dorsal fractures and fractures as low as the second lumbar vertebra. Frangeheim, in 1928, first described this condition, but aside from observations at postmortem examinations this finding had attracted no clinical attention. Three cases were reproduced by Eiselsberg and Gold. The hematoma was in the paravertebral tissues, was gradually absorbed and might be confused with a tuberculous abscess.

*Position of the Head in Intratuberculous Fracture of the Humerus.*—Kunz<sup>36</sup> reproduced roentgenograms taken in the ordinary anteroposterior position and contrasted them with pictures taken through the axilla after Iselin's method. The difference was very striking. He

34. SkrivaneK, V.: Deutsche Ztschr. f. Chir. **233**:268, 1931.

35. Eiselsberg, A., and Gold, E.: Deutsche Ztschr. f. Chir. **233**:329, 1931.

36. Kunz, H.: Deutsche Ztschr. f. Chir. **233**:441, 1931.

emphasized the necessity of taking the roentgenograms in Iselin's position. Contrary to the accepted view, the head was rotated inward by the subscapularis. The fractured surface faced forward in most cases.

*Median Nerve Injuries After Fractures of the Elbow.*—Jungbluth<sup>37</sup> felt that palsy of the median nerve in fractures of the elbow was frequently overlooked. The nerve might be completely divided, in which case exposure and suture were indicated, or it might be compressed by swelling in the antecubital fossa, where it lay in a fascial compartment. In the second instance simple incision of this fascial space might suffice.

*Periosteum, A Living Bone Suture.*—Leadbetter<sup>38</sup> reviewed a series of seventy-six cases of openly reduced fractures of long bones. In the forearm in 82 per cent of the cases that had the bone ends sutured nonunion developed, whereas in only 13 per cent of the cases in which no sutures were used did nonunion occur. The author believed that the quality of the suture was at fault. The tensile strength of sutures were tested after varying lengths of time of immersion in physiologic sodium chloride. Chromic catgut rapidly lost strength. Kangaroo tendon lost strength steadily but less rapidly than catgut. Periosteum maintained its original strength constantly. The tensile strength of periosteum lay between that of no. 2 and no. 3 chromic catgut. After experimentation with rabbits showed that the periosteal suture had osteogenic power (in the preparation of this suture care must be taken to include scrapings from the peripheral layer of cells) the sutures were tried on human cases. Some of the conclusions were: (1) autogenous periosteum had a definite tensile strength which did not vary in contact with body fluids, (2) it was easily obtained, (3) it was definitely osteogenic when properly removed, (4) it proliferated rapidly and early if the bone was poorly immobilized, and (5) mobilization at an early date was possible.

[ED. NOTE.—The editors would question whether the periosteal strip would offer a sufficiently strong suture material in adults in whom the structure often represents a thin membrane.]

*Intracapsular Fractures of the Neck of the Femur; Treatment by Internal Fixation.*—Smith-Petersen and his co-workers<sup>39</sup> described a new type of flanged nail for use in internal fixation of fractures of the neck of the femur. The advantages claimed for the nail were: (1) absolute fixation of the fragments, permitting early motion of the joint and early weight-bearing, and (2) minimum displacement of bone by the nail with resultant pressure necrosis. The technic, which was minutely

37. Jungbluth, J.: Zentralbl. f. Chir. **58**:3191 (Dec.) 1931.

38. Leadbetter, G. W.: Periosteum: Living Bone Suture, Arch. Surg. **22**:754 (May) 1931.

39. Smith-Petersen, M. N.; Cave, E. F., and Van Gorder, G. W.: Intracapsular Fractures of the Neck of the Femur, Arch. Surg. **23**:715 (Nov.) 1931.

described, consisted in exposure of the fracture through a modification of the anterior (Smith-Petersen) approach which exposed the head and neck of the femur and likewise the greater trochanter, the fragments being nailed and impacted under direct vision. The limb was suspended in light traction postoperatively and weight-bearing was permitted in a short, bivalved plaster spica holding the leg abducted as soon as the patient's general condition permitted, which was usually about three weeks postoperatively. Detailed case reports of the first twenty-four patients treated by this method were given. Twenty of the cases gave the following end-results: bony union, fifteen (75 per cent); nonunion, three (15 per cent), and deaths, two (10 per cent).

[ED. NOTE.—We believe that many surgeons have been disappointed by the results obtained from present methods of treatment in fractures of the neck of the femur. Smith-Petersen and his associates have demonstrated that it is possible to treat these injuries even when in elderly and feeble patients by open reduction with approximately the same mortality as by the closed method. By operation they secure close approximation of the fragments, and solid internal fixation. External fixation is avoided and early function permitted. Under these conditions a high percentage of complete recoveries is obtained. We believe that the method must still be regarded as *sub judice* but that it offers hope of improving on the present results.]

*Monocondylar Fracture of the Tibia.*—Bistolfi<sup>40</sup> reported fourteen cases of fracture of the tibial condyles, three of the internal condyle and eleven of the external condyle. In this article the author gave an extensive résumé of the previously reported cases, from the Continent, with the various authors' theoretical explanations of the mechanism involved. He stated that various factors existed in each case, namely, partial dislocation of the knee, a rotatory force at time of injury, or the position of the knee in either complete extension or moderate flexion. Because of these variable factors the exact mechanism involved in production of these fractures was not always the same. The author agreed with Wagner, who in 1886 stated that either the internal or the external condyle of the tibia was fractured by compression from the corresponding femoral condyle, depending on the presence of an abducting or adducting force exerted on the extended knee. This explanation fell short when the injury occurred under other conditions. Frequently, in fractures of the external condyle, there were associated ruptures or evulsions of the internal lateral and posterior crucial ligaments of the knee. Various other factors were introduced, such as the tibial spines acting as a fulcrum in the production of the external condylar fractures.

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40. Bistolfi, S.: *Chir. d. org. di movimento* 16:451 (Oct.) 1931.

## THE ETIOLOGY OF POSTOPERATIVE PEPTIC ULCERS

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One of the most serious and distressing complications following surgical treatment for benign gastroduodenal ulcerations is the postoperative peptic ulcer. Jejunal ulcers following gastro-enterostomy have been reported frequently in the literature. It appears that no method of surgical procedure offers an absolute assurance against this much dreaded complication. In 1921, Denk<sup>1</sup> reported six cases of definite peptic ulcers and eight doubtful cases following resection of the stomach. In 1925, Birgfeld<sup>2</sup> reported fifty-three cases of jejunal ulcerations following the Billroth II method of resection of the stomach. In a summary of 13,000 resections of the stomach Starlinger<sup>3</sup> reported 0.9 per cent recurrent ulcerations after the Billroth I method of resection, and 0.6 per cent jejunal ulcerations after the Billroth II method of resection.

There is a great deal of discussion in the literature concerning the etiology of this complication and the surgical methods most effective in its prevention. The main object of our work has been to study the principles involved in the mechanical and chemical factors concerned in the etiology of peptic ulcers.

In the last decade much has been written in regard to gastritis, duodenitis and jejunitis, which are found concomitant with peptic ulcerations. Some of the investigators are of the opinion that these inflammations and ulcerations of the gastro-intestinal mucosa are of infectious origin. Saunders<sup>4</sup> has recently isolated streptococci from ulcers obtained

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1. Denk, W.: Ueber Aetiologie und Prophylaxe des postoperativen Jejunalgeschwüres, *Wien. klin. Wchnschr.* **34**:2 (Jan. 6) 1921; *Studien über die Aetiologie und Prophylaxe des postoperativen Jejunalgeschwüres*, *Arch. f. klin. Chir.* **116**:1 (July 21) 1921.

2. Birgfeld, E.: Ueber das Ulcus pepticum jejuni nach Magenresektion, *Arch. f. klin. Chir.* **137**:568, 1925.

3. Starlinger, F.: Das Rückfallgeschwür nach Magenresektion wegen Ulcus ventriculi oder duodeni, *Arch. f. klin. Chir.* **162**:564, 1930.

4. Saunders, E. W.: Serologic and Etiologic Specificity of Alpha Streptococcus of Gastric Ulcer: Bacteriologic Study, *Arch. Int. Med.* **45**:347 (March) 1930.

from human material which he claims to be specific after cultural tests and agglutinations. The theory of focal infection of Rosenow has caused many "foci of infection" to be removed with the hope of curing the peptic ulcerations. Steinberg<sup>5</sup> pointed out that the focal infection, particularly in relation to the etiology of peptic ulcer, deserves a more critical interpretation. He has called particular attention to the vulnerability of the mucosa of the stomach in the presence of acid pepsin when either the local or the general resistance of the animal is lowered. This condition frequently takes place when the animal is subjected to violent experimentation, particularly the intravenous injection of various sorts of substances. It is no wonder that an army of experimental workers has been successful in producing acute lesions of the gastroduodenal mucosa, utilizing different methods of experimentation.

It is common knowledge that there are exceedingly few primary ulcers of the jejunum; it is only when the stomach is directly anastomosed with the jejunum that typical ulcers occur. Since the acid pepsin possesses bactericidal properties one would hardly expect that the surgical procedure in gastro-enterostomy would influence the growth of bacteria and that this would be the primary cause of ulcer formation. Later in our experiments it will be seen that when the acid is neutralized by the bile and pancreatic juice, no ulcers occur. It is difficult to deny, however, in view of the bacteriologic studies, particularly of Saunders,<sup>4</sup> that the infection plays some part in the chronicity of the ulcer. It is possible that a peptic ulcer offers favorable conditions for growth of the particular organism isolated by this investigator.

Silk or linen is frequently found to protrude into the gastro-enterostomy opening. Hilarowicz<sup>6</sup> expressed the belief that the secretions of the stomach may penetrate into the canal formed by the silk and produce an ulceration. That the injury caused by the silk suture may be responsible for some acute and perforated ulcerations was proved by one of our recent experiments in which two ulcerations about 4 by 5 mm. each occurred exactly where the silk penetrated the intestinal wall. However, many ulcers are found in which absorbable suture material is used, and numerous ulcers are also located remote from the line of anastomosis. We therefore hold the unabsorbable material responsible for only a very small number of postoperative peptic ulcerations.

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5. Steinberg, M. E.: Stomach Mucosa in Ulcer and in Carcinoma, *Arch. Surg.* **14**:991 (May) 1927.

6. Hilarowicz, H.: Ein experimenteller Beitrag zur Frage der Bedeutung der Seidenfäden für das Entstehen des postoperativen Jejunalgeschwürs, *Zentrallbl. i. Chir.* **10**:379, 1924.

Klose and Rosenbaum-Canné<sup>7</sup> studied the question of intestinal clamps in relation to the formation of postoperative peptic ulcers and found that they are of no importance. Ulcers are frequently found in cases in which no clamps have been used; some ulcers are located at the insertion of the mesentery and in the distal loop remote from the anastomosis, where no circulatory disturbance from the clamps could have taken place. Recently we observed a patient who was operated on for two jejunal ulcerations following gastro-enterostomy; one was located opposite the gastro-enterostomy opening at the insertion of the mesentery, and the other was found about 5 cm. from the distal end of the gastro-enterostomy opening on the anterior wall of the jejunum penetrating into the colon. The surgeon who performed the gastro-enterostomy used no clamps.

Montgomery,<sup>8</sup> in sixty-three experimental gastro-enterostomies, found four ulcers. All of these took place in the line of the anastomosis, where a hematoma was purposely produced. Since a great many ulcers are found remote from the gastro-enterostomy suture line, and some several years after the operation, the hematoma may be considered as only a casual factor in this complication.

#### CHEMICAL AND MECHANICAL FACTORS

From the time of Hunter<sup>9</sup> there have been numerous experiments to prove that the mucosa of the stomach is more resistant to the destructive power of the acid gastric juice than the other tissues. In order to study the effect of gastric juice on the jejunal mucosa, Bickel<sup>10</sup> excluded the duodenal secretions of the liver and pancreas by implanting their ducts into the abdominal wall. Utilizing this method, he obtained postoperative peptic ulcers. Exalto<sup>11</sup> reproduced in animals the same operative procedures used in man to cure gastroduodenal ulcers. He severed the stomach immediately above the pylorus and formed a posterior gastro-enterostomy either with the duodenum or the jejunum in seven cases, but was not able to produce any ulcers. On the other hand, in three of four cases he was able to produce ulcers when, in addition to the foregoing measures, he also formed a Roux anastomosis. In the last

7. Klose, H., and Rosenbaum-Canné, P.: Vergleichende experimentelle Untersuchungen über die Magennähte, *Arch. f. klin. Chir.* **124**:15, 1923.

8. Montgomery, A. H.: Gastrojejunal Ulcer: An Experimental Study, *Arch. Surg.* **6**:136 (Jan.) 1923.

9. Hunter, J.: On the Digestion of the Stomach After Death, *Phil. Tr., London* **62**:447, 1772.

10. Bickel, A.: Beobachtungen an Hunden mit extirpiertem Duodenum, *Berl. klin. Wchnschr.* **46**:1201, 1909.

11. Exalto, J.: Ulcus jejuni nach Gastroenterostomie, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **23**:13, 1911.



three cases he anastomosed the distal part of the duodenum to the large bowel, thus excluding the alkaline duodenal contents from the upper part of the jejunum, and obtained ulcers in all the cases. With the exception of the last dog, all the others received hydrochloric acid by mouth.

According to the observations of Stahnke,<sup>12</sup> jejunal ulcers were nearly always found in the distal loop of the jejunum following gastroenterostomy and lateral anastomosis. In addition to the ulcers, there was, in every case, a swollen, red mucosa covered by mucus. This condition of the mucosa was always observed sharply at the beginning of the distal portion directly within the anastomosis and reached in the distal portion exactly as far as the lateral anastomosis, or to where the duodenal contents began again to bathe the mucosa. The same condition was noted by Hertel<sup>13</sup> in a dog with a Billroth II anastomosis. Finsterer,<sup>14</sup> Schnitzler,<sup>15</sup> Lorenz and Schur<sup>16</sup> and others have emphasized the importance of using surgical procedures that reduce the acidity of the gastric contents and therefore remove one of the causes of jejunal ulcerations. These clinicians have noted the striking change in the chemistry of the contents of the stomach after resection of the stomach. Lorenz and Schur<sup>16</sup> have reviewed a series of their cases following partial gastrectomy. They have noted that the size of the antrum removed was directly proportional to the reduction of the acidity. They laid particular emphasis on the fact that the removal of the antrum does away with the part of the stomach that is indirectly responsible for the chemical phase of the gastric secretion. Steinberg, Brougher and Vidgoff<sup>17</sup> have definitely proved that the most important factors in the reduction of acidity after resection of the stomach are the rapid emptying of the stomach and the neutralization of the contents of the stomach by the influx of the alkaline juice from the duodenum. Since peptic ulcers have been reported following resection of the stomach, Finsterer<sup>14</sup> has advised removal of from three fourths to four fifths of the stomach in order to do away with part of the actual

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12. Stahnke, E.: Zur Frage der Braun'schen Anastomose, *Vereinigg. d. bayer. Chir.*, 1926; abstr., *Zentralbl. f. Chir.* **53**:2946 (Nov. 13) 1926.

13. Hertel, E.: Die Entstehungsursachen des postoperativen Jejunalgeschwürs. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **42**:57, 1930.

14. Finsterer, H.: Ueber die Bedeutung der Magenresektion beim Ulcus duodeni, *Zentralbl. f. Chir.* **52**:954, 1918.

15. Schnitzler, V.: Die Anwendung der ausgedehnten Magenresektion zur Behandlung des Magengeschwürs, *Med. Klin.* **17**:564 (May 8) 1921.

16. Lorenz, H., and Schur, H.: Unsere Erfahrungen über den Wert der Antrumresektion beim Ulcus pepticum, *Arch. f. klin. Chir.* **119**:239, 1922.

17. Steinberg, M. E.; Brougher, J. C., and Vidgoff, I. J.: Changes in the Chemistry of the Contents of the Stomach Following Gastric Operations, *Arch. Surg.* **15**:749 (Nov.) 1927.

acid-secreting area of the stomach. These surgical procedures were always based on the theory that acid pepsin was the supreme factor in postoperative jejunal ulcerations.

The postoperative jejunal ulcers following the exclusion operation introduced by von Eiselsberg, in which the pylorus was not removed, were frequent. Von Haberer<sup>18</sup> found this complication in 20 per cent of his cases, and Clairmont<sup>19</sup> in 28 per cent. These facts were of extreme importance and interest, since they emphasized not only the danger of such an operation but also its importance as an etiologic factor in jejunal ulcerations. Schur and Plaschkes<sup>20</sup> believed that in the excluded part of the pylorus the contents of the stomach and duodenum are accumulated and stimulate an increased production of acidity in the fundus.

Aschoff<sup>21</sup> has emphasized the "Magen Strasse," which is the fixed lesser curvature of the stomach, as of etiologic importance in ulcer formations. The conformation of the pyloric motor part of the stomach, the isthmus, which is the physiologic narrow pass, and the duodenal cap, which is the bumper for the peristaltic waves of the muscular pylorus, have been advanced as the cause of ulcer. Some such mechanical factors and insults find a parallel in the gastro-intestinal anastomosis. The force of the flow of the contents of the stomach, however, is not under the same control in a gastro-enterostomy as through the pylorus; the contents passing through the gastrojejunal opening may be more passive. The wall of the intestine against the stomach receives the flow of the gastric contents. The observation of Denk,<sup>1</sup> that the seat of the ulcer is on the anterior wall of the distal loop, is in agreement with the theory of a mechanical insult.

Chiari<sup>22</sup> has demonstrated that postoperative ulcers in the majority of cases are found at the insertion of the mesentery and in this way are also analogous with the location of the ulcers of the stomach along the lesser curvature, where the gastrohepatic omentum is inserted. The same author expressed the belief that the fixation of this part of the intestine to the stomach and the adhesions about the anastomosis are factors that prevent the mobility of this part of the intestine. Accord-

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18. von Haberer, H.: *Ulcus duodeni und postoperatives peptisches Jejunalgeschwür*, Arch. f. klin. Chir. **109**:413, 1918.

19. Clairmont, P.: *Ueber das Vorkommen, die Diagnose und Therapie des Ulcus pepticum jejuni*, Verhandl. d. Gesellsch. deutsch. Naturf. u. Aerzte **2**:390, 1913.

20. Schur, H., and Plaschkes, S.: *Die Bedeutung der Funktion des Antrum pylori für die Magen Chirurgie*, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **28**:795, 1915.

21. Aschoff, Ludwig: *Lectures on Pathology*, New York, Paul B. Hoeber, Inc., 1924.

22. Chiari, O. M.: *Ueber das postoperative Jejunalulcus*, Arch. f. klin. Chir. **134**:709, 1925.

ing to our own opinion, the location of the jejunal ulcers on the anterior wall or the distal loop, along the attachment of the mesentery or even in the proximal loop can be explained on the basis of mechanical factors, since the stomach and intestine are not made of inert, immovable material and vary in their position during the stages of filling and emptying and because of the changes in the intra-abdominal pressure. The method of anastomosis and the chance adhesions will also determine the location of the mechanical insults. It is therefore impossible to predict the exact part of the intestine which will receive the mechanical insult determining the location of the ulcer.

The mechanical factors may be manifold and may depend on the spastic conditions that occur about the anastomotic opening and that have been particularly emphasized by Blond.<sup>23</sup> An incarceration of the

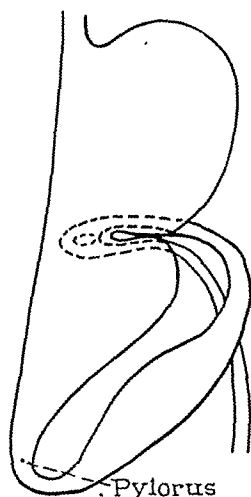


Fig. 1.—Hour-glass spasm within the anastomotic area. The proximal and distal loops of the jejunum are deeply pulled into the gastro-enterostomy opening and are pinched. (From Meyer-Burgdorff, H., and Schmidt, W.: *Der Operierte Magen*, Leipzig, Georg Thieme, 1930.

jejunum at the anastomotic opening may be caught in the hour-glass contraction of the stomach (fig. 1); there may also take place intermittent invaginations of the jejunum into the gastro-enterostomy opening or circular spasms of the distal loop of the jejunum.

Aside from the spastic condition emphasized by Blond,<sup>23</sup> we believe that the nature of the anastomosis of the intestine to the stomach predisposes to a mechanical spur formation (figs. 2 and 3). This would be the case particularly in the method of anastomosis advocated by

23. Blond, K.: Ueber den sogenannten Circulus vitiosus nach Gastroenteroanastomose, *Med. Klin.* **17**:1412, 1921; Die Beziehungen des sogenannten Circulus vitiosus nach Gastroenteroanastomose zum Ulcus pepticum jejuni postoperativum; Ein Beitrag zur Spasmogen-Ulcusgenese, *Arch. f. klin. Chir.* **135**:381, 1925.

Moise,<sup>24</sup> in which a transverse incision is made into the intestine. We have seen such a case lately, post mortem, in which the spur produced an actual obstruction of the opening into the stomach (fig. 3). Blond<sup>25</sup> expressed the opinion that such invaginations would be more frequently found if careful study were made in all cases in which there are functional complaints following gastro-enterostomies.

Nothnagel,<sup>26</sup> Leriche<sup>27</sup> and others observed that these invaginations disappear spontaneously and may also recur. Reischauer<sup>28</sup> expressed the belief that the symptoms of the vicious circle may be attributed to a titanic contraction of the upper loops of the intestine or the whole small intestine, owing to a hypertonic condition of the vagus. Dilatation, alone or combined with hypertrophy of the muscle wall of the distal fragment of the jejunum, has been observed by Steindl,<sup>29</sup> Blond<sup>25</sup>

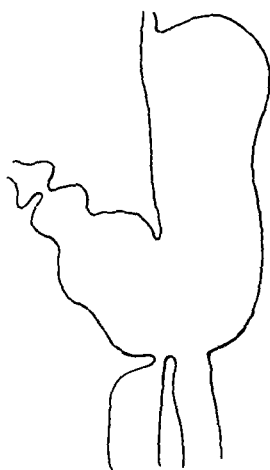


Fig. 2.—A diagrammatic presentation of the duodenal spur following a gastro-enterostomy opening. (From Meyer-Burgdorff and Schmidt.)

and many others. The dilatation distal to the gastro-enterostomy opening is limited more or less sharply and is explained on the basis of a spastic block of the distal fragment. Any one who has operated extensively on the bowel, particularly in dogs, will agree with Winkelbauer,<sup>30</sup> who called attention to anemic spots and contractions of the

24. Moise, T. S.: Gastroenterostomy with a Transverse Jejunal Incision, Surg., Gynec. & Obst. **44**:829, 1927.

25. Denk (footnote 23, first reference).

26. Nothnagel, C. W. H.: Die Erkrankungen des Darms und des Peritoneums: Ulcus duodeni simplex, Vienna, A. Hölder, 1903, vol. 5, p. 173.

27. Leriche, R.: Rev. de chir. **1**:878, 1914.

28. Reischauer, F., quoted by Hertel (footnote 13).

29. Steindl, H.: Neue Gesichtspunkte zum Problem des Enterospasmus, Arch. f. klin. Chir. **139**:245, 1926.

30. Winkelbauer, A.: Studien über die Verhütung des Ulcus pepticum post-operativum im Experiment, Arch. f. klin. Chir. **143**:649, 1926.

lumen of the small intestine due to irritation or to the introduction of a needle into the intestinal wall. The same observations have been made on various occasions by the senior author in certain irritable stomachs in which the antrum or even the omentum is pinched during an operation. The distal part of the stomach contracts in part or altogether, and this contracted condition has been mistaken for a malignant process. This was particularly true in three of our own cases, in which roentgen examination of the stomach revealed a deformity strongly suggestive of a malignant condition. We are informed of a case in which the antrum was removed by an experi-

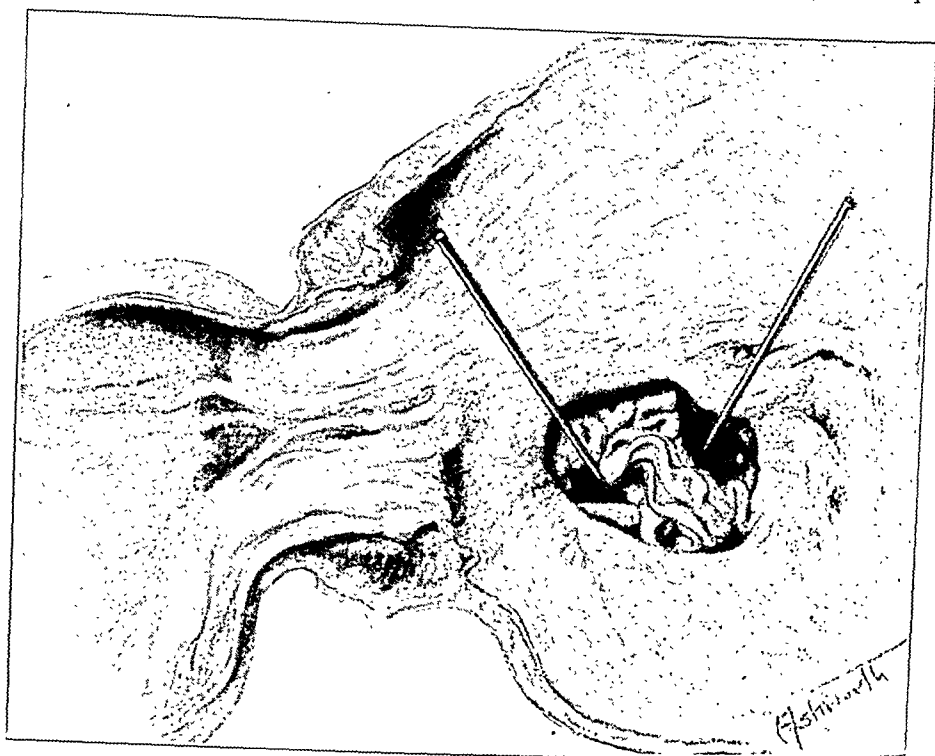


Fig. 3.—A postmortem specimen of a dilated stomach with a gastro-enterostomy demonstrating a spur formation of the jejunum into the lumen of the stomach.

enced surgeon, and a diagnosis of carcinoma was made grossly by the pathologist who was present at the operation. The condition was soon shown to be purely a spasmodic contraction.

The etiology of such jejunal invaginations into the gastro-enterostomy opening is due to local spasms. The anatomic conditions are as favorable here as in the invagination of the movable ileum into the cecum, since the jejunum is movable while the anastomosis is more or less fixed (fig. 3). In this connection we may add our own observations of several animals in which intussusception of the small intestine took place at the site of irritation from an injury of the peritoneal covering or from the presence of worms in the intestine.

It is not always possible to separate the mechanical from the chemical factors influencing the production of peptic ulcers. Kocher<sup>31</sup> believed that peptic ulcer was due to stagnation of the contents of the stomach above a contraction of the jejunum. The healing of an ulcer after perforation into the large bowel might also be explained on the same basis, as due to improved conditions of drainage.

The relation of the spastic condition of the jejunum anastomosed to the stomach to the genesis of postoperative ulcers has also been studied by Winkelbauer.<sup>30</sup> He utilized the method of Kreidel, who demonstrated on dogs that the circular and longitudinal muscle layers can be removed from large areas of the stomach and intestine without any apparent harm to the dog. The mucosa left after the muscle layers have been stripped off is sufficient protection against perforation. This procedure is similar to the Weber-Rammstedt operation for hypertrophic stenosis in infants. Winkelbauer<sup>30</sup> used Exalto's method of implantation of the duodenum into the colon, with the exclusion of a large part of the stomach, after the method of von Eiselsberg. According to Exalto,<sup>11</sup> Winkelbauer<sup>30</sup> and others, this method invariably produces an experimental peptic ulcer. In dogs in which, in addition to the foregoing procedure, he stripped off about 15 or 25 cm. of the muscle area in the distal jejunum anastomosed to the stomach, he obtained no ulcers. This experimental observation is of the greatest importance in pointing out that spastic conditions of the small intestine are directly or immediately related to the etiologic factors in the experimental production of peptic ulcers.

#### THE EXPERIMENTAL PROBLEM

As far as we know, no systematic study has been made to determine the direct influence of the motor or mechanical force of the different anatomic and physiologic subdivisions of the stomach on the experimental production of peptic ulcers. The distal part of the stomach, the pars ejestoria, is the motor and the active peristaltic factor in propelling the food. The force with which it ejects the contents of the stomach is more powerful than that in the fundus with its weak musculature. For this reason the narrow pyloric valve anastomosed to the jejunum will eject a smaller stream with a more powerful force than it would if the opening in the pyloric part of the stomach were made larger by removing the sphincter in an oblique line (fig. 10).

Another way of changing the mechanical force with which food is propelled from the stomach is to produce some form of impediment, such as a kink, in the jejunum directly under the anastomosis. Such a

31. Kocher, T.: Demonstration eines Ulcus pepticum jejuni nach Gastroenterostomie, *Verhandl. d. deutsch. Gesellsch. f. Chir.* 1:103, 1902.

procedure would directly accentuate the trauma of the propelling force of the stomach against the jejunum and at the same time produce a stagnation of the contents of the stomach above the artificial impediment.

The experimental and clinical methods used in gastro-intestinal anastomosis influence not only the mechanical but also the chemical conditions. In our experimental work we made an attempt to estimate the importance of each of these factors.

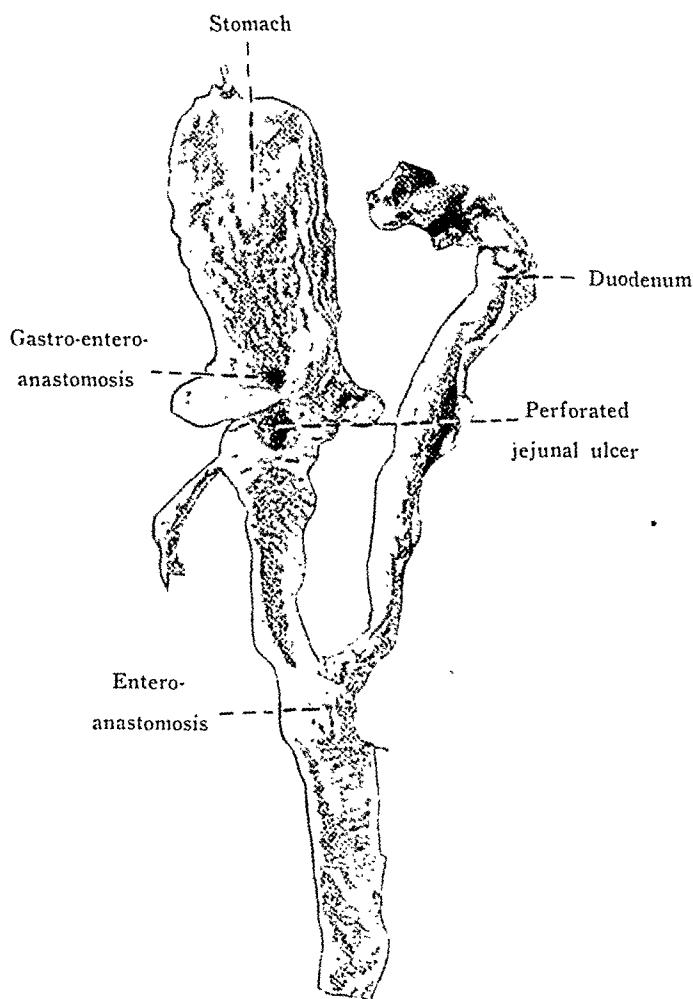


Fig. 4.—Reproduction of the original photograph of Exalto's short-circuiting operation published in 1911. (Exalto, J.: *Ulcus jejuni, nach Gastroenterostomie*, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **23**:13, 1911.)

For some time a standardized technic has been used by many investigators by which the duodenal contents can be diverted to the ileum or to the large intestine by dividing the duodenum either below or just short of the pyloric ring, closing the proximal opening, and implanting the duodenum some distance from the gastro-enterostomy opening. Mann and Williamson<sup>32</sup> published their work utilizing the

32. Mann, F. C., and Williamson, C. S.: The Experimental Production of Peptic Ulcer, *Ann. Surg.* **77**:409 (April) 1923.

same principal that Exalto<sup>11</sup> used in 1911 (fig. 4). Several of Mann's co-workers, and Mann himself, have emphasized this particular procedure and choose to call it Mann's original method of "surgical duodenal drainage." McCann<sup>33</sup> published an extensive study of experimental peptic ulcers from Mann's laboratory. In this otherwise commendable work he misquoted the figures and results of Exalto's experiments. McCann<sup>33</sup> stated that Exalto "observed jejunal ulcers, often multiple, in six of ten dogs operated on in this manner." As a matter of fact, Exalto<sup>11</sup> operated on fourteen dogs; in seven dogs he performed a gastro-enterostomy with exclusion according to von Eiselsberg, but obtained no ulcers. In four dogs he performed an exclusion operation with a "Y" anastomosis of Roux, and was able to observe three ulcers. In the last three experiments he used the same procedure except that he implanted the distal part of the duodenum into the colon. In these last three experiments he observed an ulcer in every case. In addition to the foregoing experimental procedures, he fed all the dogs, with the exception of the last one, given amounts of hydrochloric acid.

McCann<sup>33</sup> also quoted to the effect that "Exalto performed gastro-enterostomy after excluding the pylorus; he then drained the duodenal alkalis of the proximal loop into the cecum." However, McCann failed to mention that the method Exalto used is the same as that of Mann, with the slight difference that in Exalto's experiments the division was made immediately above the pylorus, while in Mann's experiments the division was made immediately beyond the pylorus. Since Exalto<sup>11</sup> published his method in 1911 (fig. 4) and obtained results later verified by Mann and others, and since Exalto's method has been used by many experimental workers and considered as a standard technic, we believe that priority is due to Exalto, and that he should receive credit for the originality of this technic. It is also our opinion that the term "surgical duodenal drainage" does not describe this procedure as well as "the short-circuiting of the duodenal contents." A reproduction of Exalto's original photograph of his operation is given in figure 4.

#### COMMENT ON THE EXPERIMENTAL DATA

One hundred dogs were used in these experiments; some of the animals died soon after the operation. If the findings were negative to ulcer formation, the animals were not included in our statistics, since two or three days, or even a week, is too short a time to allow deductions in the absence of ulcers; on the other hand, if the dogs died a few days after the operation from peritonitis or hemorrhage due to an acute perforated ulcer, this was naturally considered as positive experimental evidence of ulcer formation.

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33. McCann, J. C.: Experimental Peptic Ulcer, *Arch. Surg.* **19**:600 (Oct.) 1929.



We performed various types of gastro-intestinal anastomosis and also diverted the alkaline duodenal contents distal to the anastomosis according to the short-circuiting method of Exalto (fig. 4). At the beginning of our experiments both of these operations were performed at one stage, but later, when it was possible, the gastro-intestinal anastomosis was performed first and the short-circuiting operation at a later date. The two-stage operation gave us an opportunity to study the simple gastro-intestinal anastomosis without short-circuiting the duodenal contents. These operations therefore served as control experiments. Exalto,<sup>11</sup> Mann and Williamson<sup>32</sup> and others short-circuited the duodenal contents into the terminal ileum or the large bowel. This produces a tremendous disturbance in the physiology of the intestinal tract of the animal, which lowers its resistance, and in

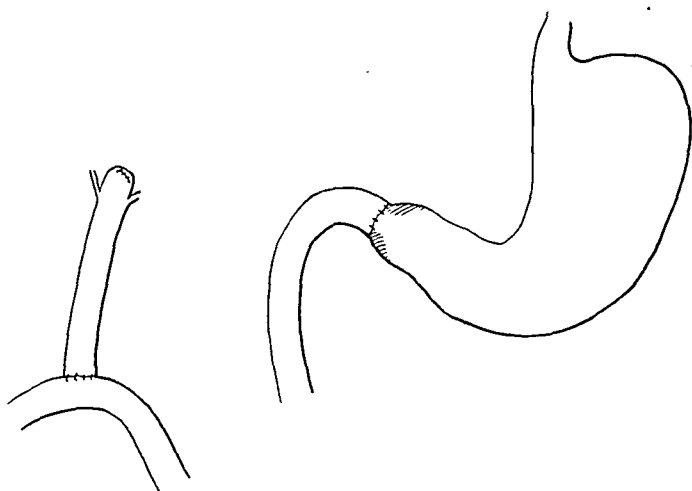


Fig. 5.—The diagram on the left shows an end-to-end gastroduodenal anastomosis with the pylorus left intact; that on the right, Exalto's short-circuiting operation.

itself is sufficient to influence the production of peptic ulcer. On account of these considerations, we implanted the distal end of the duodenum about 60 cm. from the gastro-intestinal anastomosis, allowing the bile and pancreatic juice enough of the mucosa of the area of the small intestine for the performance of their functions.

#### END-TO-END ANASTOMOSIS BETWEEN THE PYLORUS AND THE JEJUNUM WITH SHORT-CIRCUITING OF THE DUODENAL CONTENTS (FIG. 5)

Seven dogs were operated on in this manner. Ulcers developed in all of the animals; in five acute perforated ulcers developed from five to sixteen days after the operation, and death was due to either peritonitis or hemorrhage. One dog died on the fifth postoperative day, revealing an area of inflammation in the jejunum in a line with the lesser curvature of the stomach. The inflammatory area was 10 cm.

long and was covered by a diphtheritic membrane. One dog was killed on the sixty-ninth day, and a chronic indurated ulcer was found on the jejunum (fig. 6). The ulcer was 1 cm. from the gastro-intestinal anastomosis, situated on the anterior aspect of the jejunum in a line with the lesser curvature of the stomach.

These experiments demonstrate conclusively that when the alkaline duodenal contents are diverted from the end-to-end gastro-intestinal anastomosis, with the pyloric ring left intact, an ulcer develops in 100 per cent of the experiments. When we compare these results with those in which some other methods of gastro-intestinal anastomosis have been used, with less uniform results, we must naturally allow for

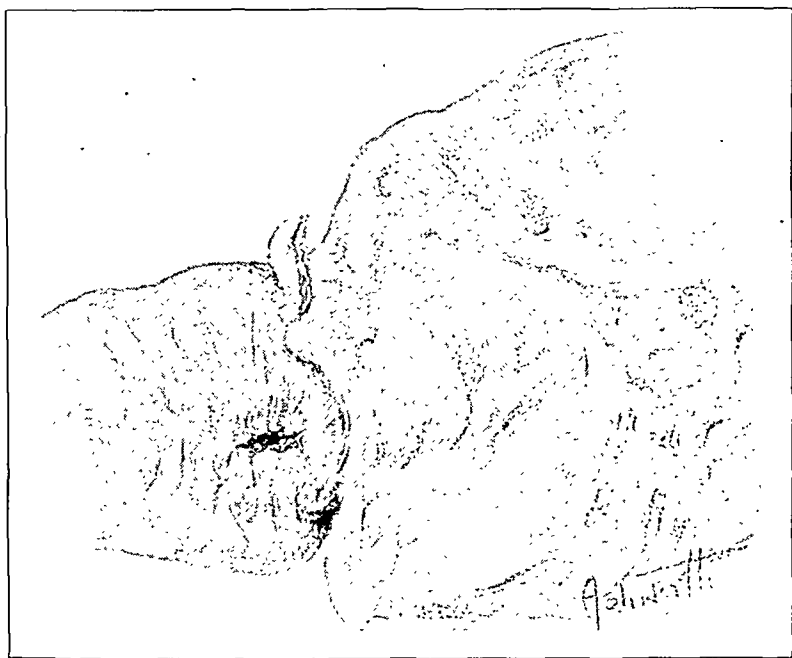


Fig. 6.—A small chronic ulcer in the jejunum following an end-to-end anastomosis between the stomach and the jejunum, and an Exalto short-circuiting operation.

additional factors contributing to the formation and chronicity of these ulcers.

The pars pylorica, which is the motor part of the stomach, possesses a thick muscle wall; it engages in active peristaltic movements and propels the contents of the stomach forcibly through a narrow pyloric ring into the jejunum, which is anastomosed end-to-end. Digestion of the jejunal mucosa would be expected at the place where the acid chyme constantly strikes the mucosa and produces a rather localized mechanical and chemical trauma. The location would depend not only on the method of anastomosis but on the chance position the jejunum may assume due to adhesions and other factors not under the surgeon's control.

In two animals the ulcers were on the anterior jejunal wall; in two others they were on the posterior and anterior jejunal walls, and in three dogs the ulcers were on the jejunal side on a line with the lesser curvature of the stomach.

It is quite possible that more chyme strikes that part of the jejunum which is directly anastomosed to the terminal part of the lesser curvature than any other part. The function of the lesser curvature has been elaborated, particularly by Aschoff.<sup>21</sup>

In one animal, not included in the foregoing experiments, an obstructive jaundice developed from obstruction of the common duct due to invagination of the proximal closed end of the duodenum. It died three days after the operation from hemorrhage due to numerous erosions of the mucosa of the stomach (fig. 8). This demonstrates that in experimentally produced obstructive jaundice, in the presence

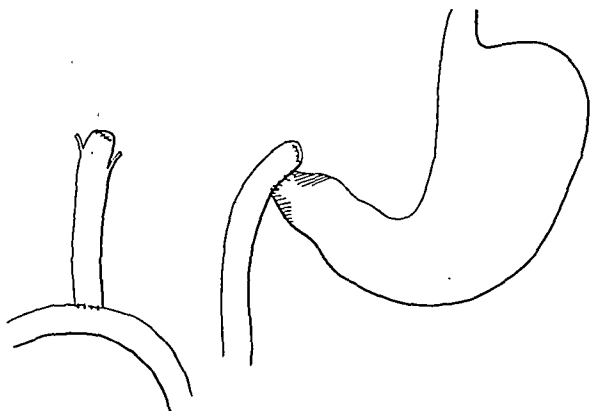


Fig. 7.—The diagram on the left shows an end-to-side gastrojejunal anastomosis with the pylorus left intact; that on the right, Exalto's short-circuiting operation.

of the Exalto short-circuiting operation, when the acid values of the stomach are high, erosions may form and cause a fatal hemorrhage.

#### TERMINOLATERAL GASTRO-INTESTINAL ANASTOMOSIS WITH THE PYLORUS LEFT INTACT (FIG. 7)

In this series of experiments the usual Exalto short-circuiting operation was performed, the distal end of the duodenum being implanted into the small intestine about 60 cm. from the pylorus. The pylorus was then anastomosed to the jejunum end-to-side. Of the animals operated on in this manner, seven have survived long enough to enable us to draw certain conclusions. In three dogs typical chronic ulcers developed in the jejunum. The observation of these animals lasted from four to ninety days. In one dog perforated ulcer developed on the posterior wall of the jejunum next to the anastomosis, and it died seven days after the operation. One dog was killed at the end of fifty-seven days and another at the end of sixty-seven days, and no ulcers were found.

This form of anastomosis produced ulcers in only about 43 per cent of our experiments, and most of the ulcers were chronic. The locations of the ulcers were opposite the opening of the pylorus, corresponding to the lesser curvature of the stomach (fig. 9). The chronicity of the ulcers in these cases, in contradistinction to the acute perforating type in the end-to-end anastomosis, can be attributed to the fact that



Fig. 8.—Erosions of the mucosa of the stomach following Exalto's short-circuiting operation and an end-to-end anastomosis between the stomach and the jejunum, with accidental obstructive jaundice.

an end-to-side anastomosis allows much more room for the impact of the chyme of the stomach from the pyloric opening. The location of the ulcers opposite the pyloric opening is evidently due to trauma, since in the end-to-side anastomosis the relative position between the opening in the stomach and the jejunum can be more easily controlled (fig. 7).

As explained, the position of the proximal jejunal wall in the end-to-end anastomosis is more capricious, and the location of the ulcer will vary according to the position of the jejunum. On account of the weight of the distal jejunal loop, the anterior wall of the jejunum will be closer to the opening of the pylorus (fig. 5).

An additional factor influencing the production of experimental ulcers is to be found in the degree of acidity and in the emptying time of the contents of the stomach. The lumen of the dog's jejunum is quite narrow, and the end-to-end anastomosis between the latter and

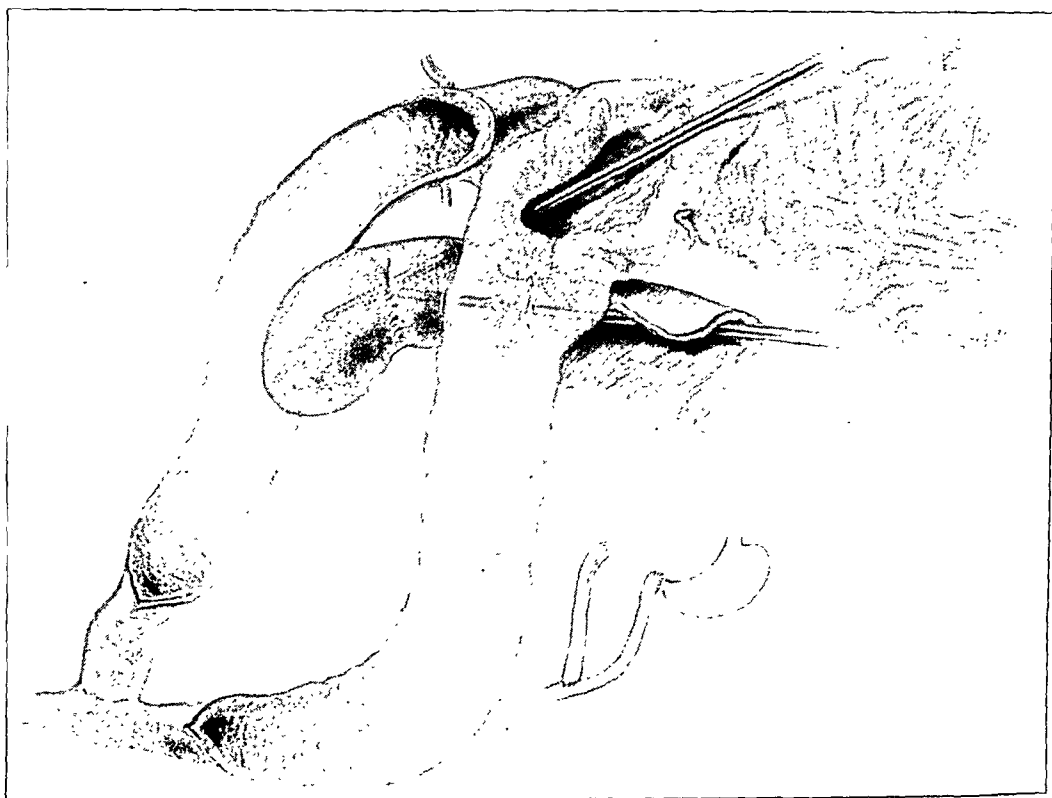


Fig. 9.—A large, chronic, indurated ulcer in the jejunum perforated into the appendix following an end-to-end anastomosis, with the pylorus left intact, and the usual Exalto short-circuiting operation.

the pylorus will shrink and become much narrower than the opening in the end-to-side anastomosis. For this reason the emptying time will be delayed and the degree of acidity will be higher in the end-to-end anastomosis. This was actually demonstrated in chemical examination in the various types of operations on the stomach. (Some of the chemical studies are to be published at a later date.)

TERMINOLATERAL JEJUNAL ANASTOMOSIS WITH A MINIMUM PART  
OF THE PYLORUS OF THE STOMACH REMOVED (FIG. 10)

In these experiments we attempted to change the mechanical and chemical factors. The usual Exalto short-circuiting operation was

performed, the alkaline contents of the duodenum being diverted from the gastro-intestinal anastomosis. The distal 2 cm. of the pyloric portion of the stomach, including the pyloric valve, was removed. The incision into the stomach was made in an oblique line from the lesser curvature on the right side to the greater curvature to the left (fig. 10). In this manner the terminolateral anastomosis was made wide without sacrificing too much of the stomach. This procedure not only enlarged the gastro-intestinal anastomosis, but also partially paralyzed the propelling force of the stomach by removing a part of its motor pyloric end. The emptying time of the contents of the stomach in this operation is more rapid than in the previous methods of anastomosis, and the degree of acidity is lower.

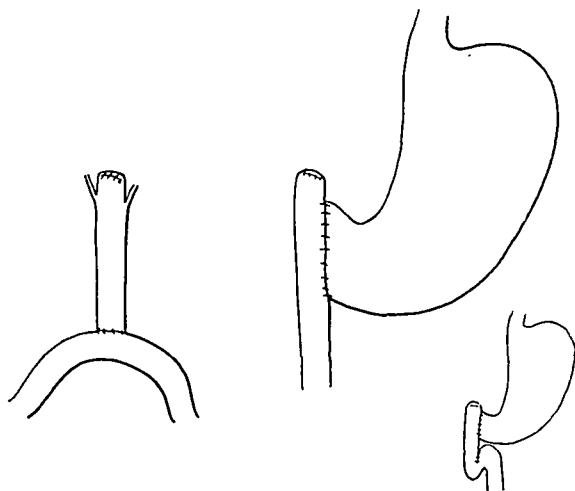


Fig. 10. The diagram on the left shows an end-to-side gastrojejunal anastomosis, with a minimal part of the pylorus removed; that in the center, Exalto's short-circuiting operation, and that on the right, a kink 5 cm. distal to the anastomosis.

Of these animals, sixteen have survived long enough to demonstrate the effect of this surgical procedure on ulcer formation. All of the animals were alive for from thirty-two to seventy-five days. Most of them were operated on in two stages. Chronic jejunal ulcers developed in only two dogs.

In three dogs the jejunum next to the anastomosis was markedly inflamed; eleven dogs showed no evidence of inflammation or ulcers in the period of observation of from thirty-seven to seventy-five days.

This operation, in which only part of the pylorus is removed, throws more light on the factors concerned in the production of experimental peptic ulcers. The partial paralysis of the motor force of the pylorus, the rapid emptying of the contents of the stomach and the lessened degree of acidity have prevented the formation of ulcers in fourteen of sixteen dogs operated on in this manner.

In dog 33 the ulcer was 5 by 1 cm. in diameter and had indurated edges; it was situated on the anterior wall of the jejunum at the proximal end of the anastomosis, again corresponding with the line of the lesser curvature (fig. 11).

Dog 8 was killed on the thirty-second day. Three ulcers of various sizes were found in the jejunum, all on the posterior wall. One was found directly at the anastomosis, another one at the distal part of the anastomosis, and one about 5 cm. from the distal end of the anastomosis (fig. 12). This demonstrates that the location of the ulcers

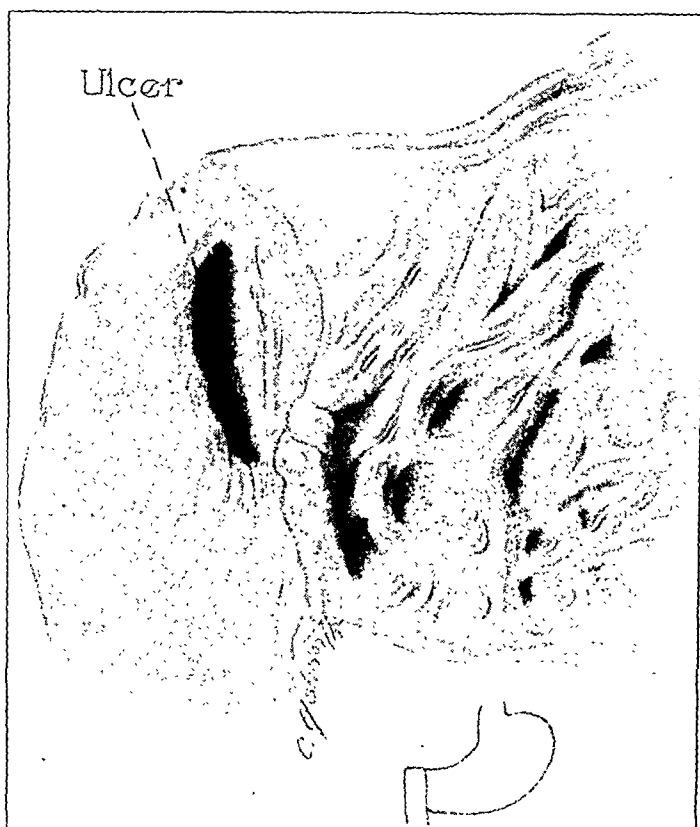


Fig. 11.—A chronic ulcer in the jejunum, with overhanging of the distal edge following an end-to-side gastrojejunal anastomosis with the removal of a minimal part of the pylorus, and an Exalto short-circuiting operation.

may vary, since the factors of mechanical and chemical trauma are not always under experimental control.

Only artificially produced kinks may determine the location of the ulcer (fig. 13).

#### SUBTOTAL GASTRIC RESECTION WITH VARIOUS BILLROTH GASTRO-INTESTINAL ANASTOMOSES AND THE EXALTO SHORT-CIRCUITING OPERATION (FIG. 14)

In the foregoing experiments we have attempted to determine what influence the removal of only a small part of the motor part of the

stomach has on the formation of jejunal ulcers. In the series to be described we have proceeded with the resection of more than the distal muscular part, leaving only the proximal one-third. The remaining part of the stomach has the function of active secretion of gastric juice, and exhibits only tonic contractions. As in all our previous experiments, we have in this instance diverted the alkaline duodenal contents from the gastrojejunal anastomosis, using the short-circuiting method described by Exalto.<sup>11</sup> Twelve anastomoses were performed after the



Fig. 12.—Several acute ulcerations, one perforated, following an end-to-side anastomosis between the stomach and the jejunum, with a minimum part of the pylorus removed, and the usual Exalto short-circuiting operation (a).

method of Finsterer-Hoffmeister (fig. 14 *B*), two after the method of Polya (fig. 14 *A*) and six after the Billroth I method modified by von Haberer, in which the large lumen of the stomach was made small in order to enable us to anastomose it end-to-end to the jejunum (fig. 14 *C*). Ulcers developed in none of these animals, with the exception of two of six operated on according to the method of von Haberer. In these two cases the lumen in the gastro-intestinal anastomosis was not



larger than 1 cm. in diameter, and only the distal half of the stomach was removed. All of these dogs were observed for a long period of time—some as long as three months. In analyzing the factors that have prevented the formation of ulcers in the dogs operated on according to the Billroth II method, we wish to call particular attention to the fact that the whole muscular, motor and propelling part of the stomach was removed, and that the anastomosis between the stomach and the

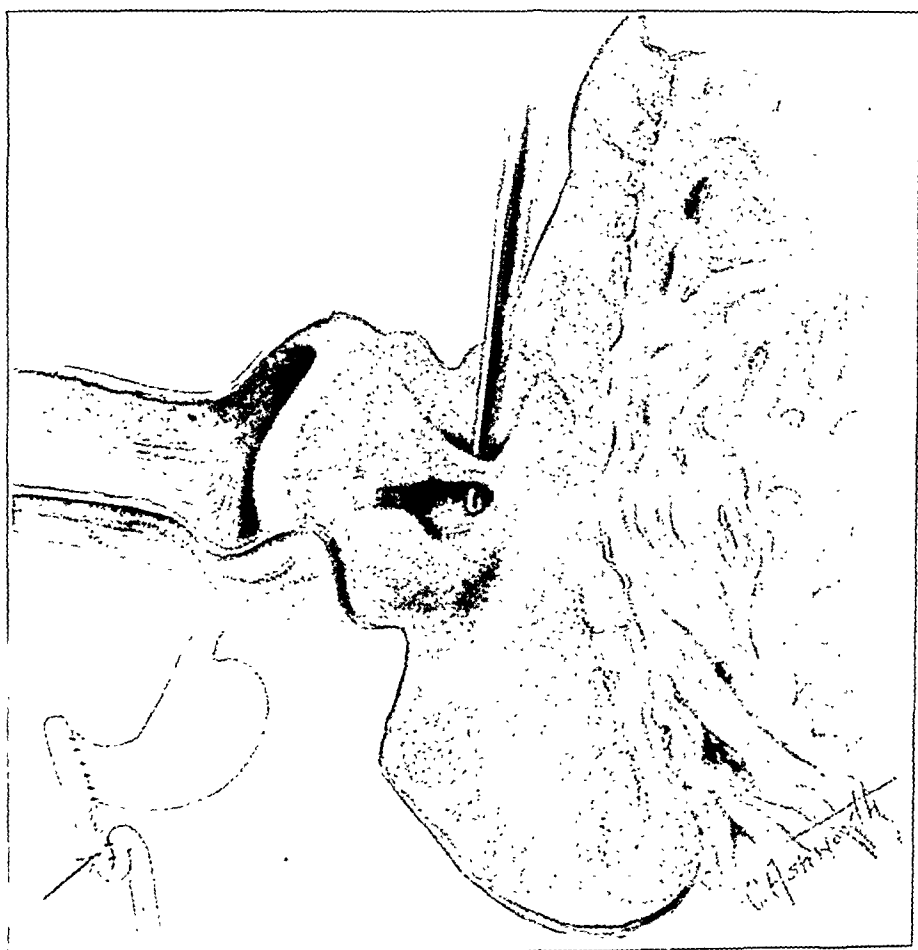


Fig. 13.—An undermined ulcer following an end-to-side anastomosis between the stomach and the jejunum, with a minimal part of the pylorus removed. The ulcer occurred only after a kink was made in the jejunum. The usual Exalto's short-circuiting operation was also performed.

intestine was made wide. Such a procedure eliminates the periodic localized trauma by acid stomach contents against the jejunum and produces a rapid but rather passive emptying of the stomach.

The variation of the chemical factors in this series of experiments should be taken into consideration, since the emptying time is hastened. It should not be forgotten that in removing a larger part

of the stomach than the antrum, some of the acid-secreting fundus glands are also removed. On the other hand, the short-circuiting operation of Exalto removes the bile and pancreatic juice, and therefore the reaction of the contents of the stomach, in spite of the large resection, is never completely anacid (Steinberg, Brougher and Vidgoff<sup>17</sup>).

Evidence that the mechanical factors, in the presence of unneutralized acid pepsin, influence the formation of ulcer can be substantiated by two of this series of experiments, in which a modified von Haberer anastomosis was performed with a narrow lumen and the removal of

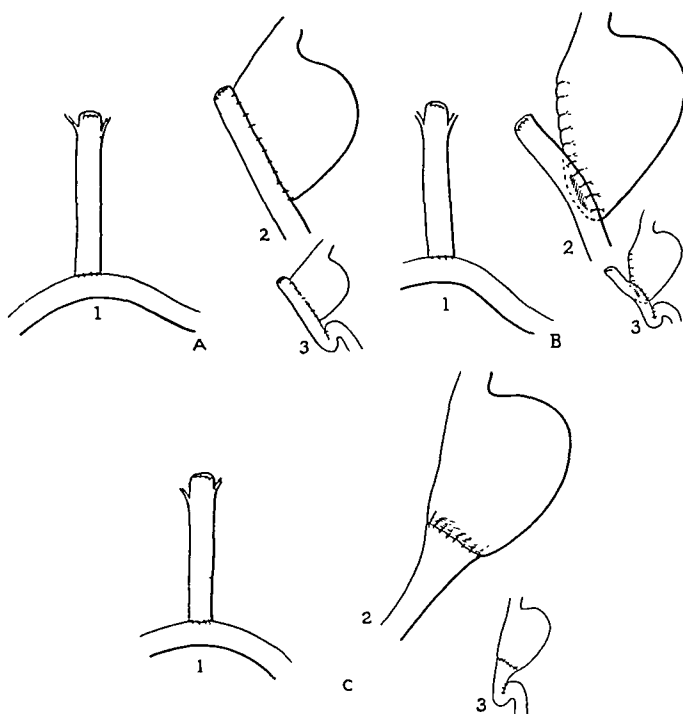


Fig. 14.—In *A*, 1 shows a subtotal resection of the stomach according to the method of Billroth II modified by Polya; 2, Exalto's short-circuiting operation; 3, a kink made 5 cm. distal to the anastomosis. In *B*, 1 shows a Billroth II resection of the stomach modified by Finsterer; two thirds of the stomach was removed; 2, Exalto's short-circuiting operation diverting the alkaline duodenal contents distal to the anastomosis; 3, a kink 5 cm. distal to the anastomosis. In *C*, 1 shows a subtotal resection of the stomach according to the Billroth I method modified by Haberer; 2, Exalto's short-circuiting operation; 3, a kink 5 cm. distal to the anastomosis. The gastro-intestinal stoma is actually much smaller than is presented in this diagram.

a smaller part of the stomach. A small ulcer developed in the jejunum in two of the six dogs operated on according to this method (fig. 15). In the end-to-end anastomoses according to von Haberer, the narrow lumen also tends to retard the emptying time of the stomach, and there-

TABLE 1.—*Summary of the Various Experimental Procedures*

Type of Operation	Number of Operations	Number of Ulcers	Percentage of Ulcers	Comment
Control experiments, including various types of gastro-intestinal anastomoses with the Exalto short-circuiting operation left out	30	0	0	
Kink in the duodenum distal to the pylorus	2	0	0	Duodenal mucosa inflamed in one dog
End-to-end anastomosis between the jejunum and the stomach with the pylorus left intact and with Exalto's short-circuiting operation, see figure 5	7	7	100	One dog developed jaundice and died from hemorrhage due to erosions of the gastric mucosa
End-to-side anastomosis between the stomach and jejunum with the pylorus left intact and an Exalto short-circuiting operation; see figure 7	7	3	43	
End-to-side anastomosis between the stomach and the jejunum with the pylorus left intact and Exalto's short-circuiting operation; a kink was made in the jejunum 5 cm. distal to the anastomosis	1	1	100	
End-to-side anastomosis between the stomach and the jejunum with a minimal part of the pylorus removed and an Exalto short-circuiting operation; see figure 10	16	2	12.5	In three dogs the jejunum was markedly inflamed
End-to-side anastomosis between the stomach and jejunum with a minimal part of the pylorus removed; a kink 5 cm. distal to the anastomosis, and Exalto's short-circuiting operation	3	3	100	
Anastomosis between the stomach and the jejunum with a resection of one half of the stomach; a Billroth I method, end-to-end modified by von Haberer, and an Exalto short-circuiting operation; see figure 14 C	6	2	33	This is not a true von Haberer type of Billroth I, since the stomach is anastomosed to the jejunum end-to-end
Anastomosis between the stomach and the jejunum with a resection of one half of the stomach; a Billroth I method, end-to-end modified by von Haberer, and an Exalto short-circuiting operation; a kink made 5 cm. distal to the gastro-intestinal anastomosis; see figure 14 C	4	2	50	This is not a true von Haberer type of Billroth I, since the stomach is anastomosed to the jejunum end-to-end
A subtotal resection of the stomach and an anastomosis between the stomach and the jejunum, end-to-side, according to the Billroth II modified by Finsterer-Hoffmeister and an Exalto short-circuiting operation; see figure 14 A and B; two Polya included	14	0	0	
A subtotal resection of the stomach and an anastomosis between the stomach and the jejunum, end-to-side, according to the Billroth II modified by Finsterer-Hoffmeister and an Exalto short-circuiting operation; a kink made 5 cm. distal to the gastro-intestinal anastomosis; see figure 14 B	6	0	0	

fore, the acidity of the contents of the stomach is maintained at a high level (table 2).

The mechanical and chemical factors cannot be easily separated, since one may influence the other. These interrelations will be demonstrated in other experiments, which are to follow immediately, and in more chemical examinations made during the course of experiments, which will be published at a later date.

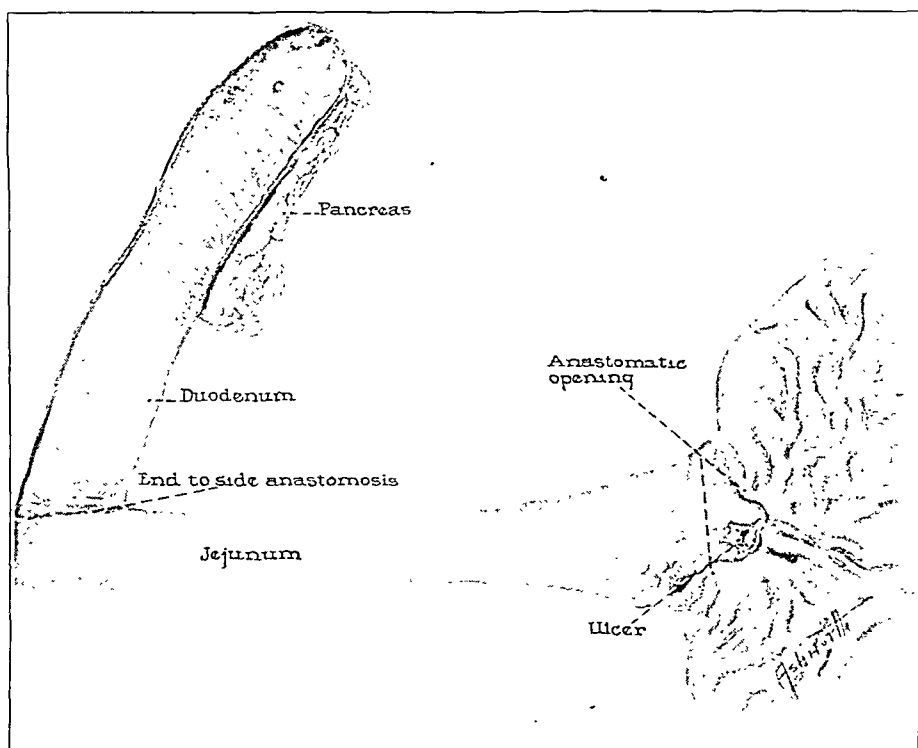


Fig. 15.—A small chronic ulcer in the jejunum about 2 cm. from the termination of the lesser curvature. The Billroth I method of end-to-end anastomosis modified by Haberer was used, the distal half of the stomach being removed.

#### PARTIAL OBSTRUCTION AS A FACTOR IN THE ETIOLOGY OF PEPTIC ULCER

In the last few months of our work we introduced new factors to throw more light on the genesis of the postoperative, experimentally produced ulcers. In some of the animals in which ulcers did not develop during the various operative procedures used, we performed a kinking in the intestine 5 cm. distal to the gastro-intestinal anastomosis. Such a procedure can produce an actual mechanical impediment against a forcible ejection of acid chyme, causing it to stagnate for variable periods of time. It was thought that the results of such a partial obstruction would help us greatly in analyzing the various mechanical and chemical factors on the part of the stomach and jejunum. All the

dogs operated on in this manner, with the exception of two controls, had undergone the Exalto short-circuiting of the alkaline duodenal contents. In two animals the anatomic relations of the stomach and duodenum were left intact, and the duodenum was kinked about 5 cm. distal to the pylorus. One dog was killed at the end of nine days and the other at the end of forty-six days. No definite ulcers were seen, except that in a dog that was observed nine days there was a small reddened area about 1 cm. in diameter on the posterior wall of the duodenum proximal to the kink.

One animal that had undergone terminolateral anastomosis between the stomach and the jejunum (the pylorus was left intact) and the Exalto short-circuiting operation was explored at the end of sixty-seven days, and no evidence of ulcer was found (fig. 7). A kink

TABLE 2.—*Chemical Studies of the Stomach Contents After Various Gastro-Intestinal Anastomoses\**

Dog 85			Dog 66		
Billroth II method modified by Finsterer—wide stroma (fig. 14 B)			End-to-end anastomosis between stomach and jejunum, modified after von Haberer's method of Billroth I—narrow stroma (fig. 14 C)		
Meal given at 4 p. m.			Meal given at 8 p. m.		
Time of Examination	Free Acidity	Total Acidity	Time of Examination	Free Acidity	Total Acidity
4:15	0.0000	0.0273	8:15	0.0000	0.0729
4:30	0.0000	0.0273	8:30	0.0000	0.0820
4:45	0.0000	0.0456	8:45	0.0456	0.1459
5:00	0.0000	0.0456	9:00	0.1003	0.2918
5:15	0.0000	0.0364	9:15	0.1094	0.3007
5:30	Stomach empty		9:30	Stomach empty	

\* The test meal consisted of 50 Gm. of hamburger steak brought to a boil in 200 cc. of water.

was made 5 cm. distal to the anastomosis between the stomach and the jejunum. This animal died five days after the partial obstruction was created, from peritonitis due to a perforated ulcer proximal to the kink.

Three dogs that had undergone a minimum resection of the pylorus with an end-to-side anastomosis between the stomach and the jejunum and also an Exalto short-circuiting operation were observed for a period of from thirty-seven to seventy days (fig. 10). These three dogs were explored, and no ulcers were found. A kink was made in all of the animals 5 cm. distal to the terminolateral anastomosis (fig. 13). In each one of these animals ulcers developed in the jejunum. Dog 60 was examined seventy days after the kink was made, and an indurated scar was found at the jejunum next to the greater curvature of the stomach. Dog 38 was killed forty days after the kink was made, and a small ulcer 5 by 7 mm., with indurated edges, was found on the posterior surface of the jejunum just proximal to the kink. In dog 43

acute peritonitis developed seven days after the kink was made. The exploratory incision in the wall of the stomach gave way; an ulcer 1 cm. in diameter just proximal to the kink was found.

The animals that were subjected to subtotal gastric resection, four according to the Billroth I, end-to-end method, modified by von Haberer (fig. 14 *C*), and six according to the Billroth II method, modified by Finsterer (fig. 14 *B*), with an Exalto short-circuiting operation, were explored after two or three months of observation, and no evidences of ulceration were found. We performed a kink in each one of these animals 5 cm. distal to the gastro-intestinal anastomosis. The animals were observed from twenty-seven to sixty days and then killed. In two dogs operated on according to the Billroth I, end-to-end method, modified by von Haberer, ulcers developed (figs. 14 *C* and 15).

Though these experiments are not numerous, yet they demonstrate definitely the importance of certain indisputable facts. When the muscular, pyloric part of the stomach was left intact, or partially removed, and a terminolateral anastomosis was performed, together with an Exalto short-circuiting operation, and when no ulcers were found, ulcers developed in all the dogs when an impediment to the flow of the acid chyme was made in the form of a partial obstruction. On the other extreme is the absence of ulcers in subtotal resection with a Billroth II anastomosis, an Exalto short-circuiting operation and a kinking. Again, the factors concerned in these experiments are evidently the propelling of the acid chyme by the muscular pylorus with a certain force against an impediment distal to the anastomosis. How much the stagnation of the acid chyme is responsible for the ulcer formation is difficult to estimate. The striking fact that no ulcers were present in any of the animals subjected to subtotal gastrectomies according to the Billroth II method again supports the view that it is in part the absence of the *vis a tergo* of the pyloric part of the stomach which is responsible for the lack of ulcer formation in the dogs on which subtotal resection is performed. It is true, as mentioned, that after a subtotal gastrectomy according to the Billroth II method a part of the actual acid-secreting area of the stomach is also removed, and the rapid emptying time reduces the acidity of the contents of the stomach.

#### CONTROL EXPERIMENTS

Our belief that chemical and mechanical factors are primarily responsible for the formation of experimental peptic ulcer is supported by the control experiments in which we performed the various forms of gastro-intestinal anastomosis, leaving out the Exalto short-circuiting operation. This allowed the alkaline duodenal contents the opportunity to neutralize the acid contents at the site of gastro-intestinal anastomosis.

There were thirty dogs in this series; they were observed for a period of from nineteen to sixty days. None of them showed any evidence of ulcer formation. As soon, however, as the Exalto short-circuiting operation was performed, in some of the dogs, ulcer formation took place.

#### COMMENT

The factors concerned in the etiology of the experimentally produced, postoperative peptic ulcers have been discussed in a review of the literature and in the protocols of our experiments. It remains only to crystallize and coordinate the accumulated data.

Thirty control experiments with the various gastro-intestinal anastomoses have not yielded a single ulcer. It was only when the gastro-intestinal anastomosis was subjected to the acid gastric contents, which were prevented from being mixed with the alkaline duodenal contents, that peptic ulcer occurred. It is therefore quite evident that acid pepsin is of the greatest importance in the causation of the experimentally produced ulcer. The mechanical factors are somewhat more difficult to analyze, since the various operations on the stomach bring about some change in the acidity of its contents. There were, however, two types of experiments in which we did not expect much change in the chemical factors, while the forms of gastro-intestinal anastomoses were different. In the end-to-end anastomosis between the stomach and the jejunum, with the Exalto short-circuiting operation, ulceration developed in all the animals (fig. 5), while in the end-to-side anastomosis they developed in only 43 per cent (fig. 7). It is therefore the direction of the jejunum and the method of anastomosis which furnish the evidence of the mechanical factor. In the end-to-end anastomosis it is possible that the weight of the jejunum brings its anterior wall closer to the pyloric opening than in the end-to-side anastomosis. Another factor to be considered is the blood supply, which is less disturbed in the end-to-side anastomosis.

When only a minimum part of the pyloric end of the stomach was removed, definite ulcers developed in only two of sixteen dogs. In this particular series of experiments it is difficult to separate the chemical from the mechanical factors and to evaluate each accordingly. It has, however, been demonstrated (Steinberg, Brougher and Vidgoff<sup>17</sup>) that after resection of the stomach in which there is also an Exalto short-circuiting operation the contents of the stomach remain acid. The lack of uniform ulcer formation in this form of anastomosis can be explained by the size of the opening of the stomach, which is wider, and the partial paralysis of the propelling force of the pyloric end of the stomach, which has been partly removed. The traumatic factor has therefore been minimized by this procedure and only after a kink was produced 5 cm. distal to the gastro-intestinal opening did ulceration take

place in each dog so operated on. The additional chemical and mechanical factors in this operation were therefore in the intestine, where an actual partial impediment to the flow of the gastric contents enhanced the trauma and also produced a stagnation of the acid contents.

In two of six animals operated on according to the Billroth I, end-to-end method, modified by von Haberer, ulceration developed in the jejunum (figs. 14 C and 15). This was considered as important evidence of mechanical and chemical factors, since the gastro-intestinal opening was very narrow, causing a delayed emptying and a higher acidity of the contents of the stomach (table 2). The absence of ulcers in the series of experiments with the Billroth II method of anastomosis is evidently due to the lack of *vis a tergo* of the stomach, since its muscular pyloric part has been removed. The additional factors considered are the reduced areas of acid-secreting glands which take place in a wide gastro-intestinal anastomosis after a subtotal resection of the stomach.

We have emphasized the traumatic, mechanical and chemical factors in ulcer formation and have taken into consideration the motor drive of the pyloric end of the stomach, the artificial impediment in the jejunum and the width of the anastomotic opening. The invagination of the jejunum into the stomach, which Blond considered as important in the traumatic theory of postoperative ulcer formation, could not have taken place in our experiments with the pylorus intact, since the jejunum could not have invaginated into such a small opening. On the other hand, if the jejunum did invaginate, in our experiments with subtotal resection of the stomach according to the Billroth II method, it was not evidently of great importance, since no ulcers took place in this series of operations. It was impossible in our experiments to evaluate the spasms of the jejunum as of etiologic importance.

The postoperative jejunal ulcers reported following resection of the stomach in the human subject do not evidently correspond to the absence of such ulcers in the dog, in spite of the artificially heightened acidity of the contents of the stomach. This could perhaps be explained by the inherent susceptibility of the human being to ulcer formation. In spite of the difference in the susceptibility of man and the dog to ulcer formation, our experimental work nevertheless emphasized certain factors that will tend to prevent jejunal ulcers in man. The Roux method of anastomosis, either with a gastro-enterostomy or with a subtotal resection of the stomach, diverts the alkaline duodenal contents from the gastro-intestinal opening and influences the formation of postoperative peptic ulcer. After eight subtotal resections of the stomach with the Roux anastomosis, Finsterer (personal communication) reported that postoperative jejunal ulcers developed in seven patients. Finsterer succeeded in curing these patients with jejunal ulcers only after he undid the Roux



anastomosis and restored some of the wall of the stomach. The same argument can be put forward for the lateral entero-anastomosis, which is used to prevent stasis in the proximal loop. The intention of this operation, as in the Roux operation, is to drain the alkaline duodenal contents away from the gastro-anastomotic opening. The reason, however, that the Roux anastomosis and the entero-anastomosis do not give a higher percentage of jejunal ulcers is due to the fact that in spite of the intention of the surgeon to divert the alkaline duodenal contents away from the gastro-anastomotic opening, bile and pancreatic juice find their way into the stomach. The absence of frequent jejunal ulcers after a subtotal resection of the stomach with anticholic anastomosis and the lateral entero-anastomosis may be explained, in addition to the already mentioned factors, also on the basis of the removal of a larger acid-secreting area. The latest statistics (Starlinger<sup>3</sup>) report that the Billroth II resection of the stomach gives 0.6 per cent of jejunal ulcers. From our experimental evidence it would seem that the removal of a large part of the stomach not only causes a low acidity of the stomach contents, owing to the rapid emptying and regurgitation of the alkaline duodenal contents and the actual reduced area of acid-secreting stomach, but also does away with a large part of the stomach with its motor-propelling force. Our experiments would also emphasize that the avoidance of kinks distal to the gastro-anastomosis opening and a wider gastro-intestinal anastomosis will be of some prophylactic value in preventing postoperative jejunal ulcers.



#### SUMMARY

One hundred dogs were subjected to various methods of gastro-intestinal anastomosis in order to study the etiologic factors responsible for the formation of postoperative peptic ulcer.

The acid gastric juice of the stomach was prevented from being neutralized by the alkaline duodenal contents by using the short-circuiting operation of Exalto. Exalto, Mann and Williamson and others short-circuited the duodenal contents into the terminal ileum or the large bowel. This produces a tremendous disturbance in the physiology of the intestinal tract of the animal, which lowers its resistance and in itself is sufficient to influence the production of peptic ulcer. On account of these considerations we implanted the distal end of the duodenum about 60 cm. from the gastro-intestinal anastomosis, allowing the bile and pancreatic juice enough of the mucosa of the small intestine area for the performance of their functions.

It was demonstrated that the corrosive action of the acid pepsin in the presence of certain mechanical factors produces peptic ulcerations.

The muscular pyloric part of the stomach propelling the acid contents of the stomach through the pyloric opening may be responsible for the actual localized trauma of the jejunum.

An impediment in the form of a kink in the distal loop of the jejunum or a narrow gastro-intestinal opening favors the development of a jejunal ulcer. These procedures cause a delay in the emptying time and an increased acidity in the contents of the stomach.

Ulcers found immediately in front of a kink also demonstrate that there is a direct mechanical trauma determining the location of the ulcer.

It was conclusively demonstrated that a subtotal resection of the stomach with a wide stoma, performed according to the Billroth II method (Finsterer-Hoffmeister), has never been followed by a peptic ulcer, in our experiments, even in the presence of an artificial kink in the jejunum. This we consider of scientific and clinical interest and importance. On the other hand, the Billroth I method of anastomosis, end-to-end, and the minimal resection of the stomach according to the Billroth II method have given rise to jejunal ulcers, particularly when artificial kinks have been added where no ulcers were originally found. There is, nevertheless, a difference between the experimental method of Billroth I anastomosis, end-to-end, modified by von Haberer, as used in our investigations and the one used in the clinic. In the experimental method the stomach is anastomosed to the very narrow jejunum of the dog, while in the clinical application the stomach is joined to a wider duodenum end-to-end. This will explain the good results obtained by von Haberer in his modified Billroth I method of resection of the stomach.

Only a few of the methods practiced in the surgical treatment for gastroduodenal ulcers were used in our experiments. It is therefore possible that there are variations of the chemical and mechanical factors in other operative procedures, or even in the procedures we used in dogs when applied to the human subject. In this connection we might mention Blond's theory of the invagination of the jejunum into the gastro-intestinal opening, also the spasm of the jejunum. Variation in the predisposition of the subject based on the neurogenic theories that may influence the degree of the psychic secretion and motility of the gastro-intestinal tract should also be taken into consideration.

Many of our experimental procedures are used by the surgeon in treating gastroduodenal ulcerations, and we therefore believe that our data emphasize the fact that a large anastomotic opening between the jejunum and the fundus of the stomach is the best method to prevent jejunal ulcerations.

Kinks in the distal jejunum following gastro-anastomoses should be avoided.

In case an end-to-end anastomosis is necessary in resection of the jejunum for jejunal ulcer, the end-to-end anastomosis should not be placed distal to the gastro-anastomosis, because it may produce the same stasis of the gastric contents in the distal jejunum as a kink.

The entero-anastomosis of Braun, and particularly the "Y" anastomosis of Roux, should be avoided, because these methods, particularly the last one, drain the alkaline duodenal contents away from the gastro-anastomosis. If a Roux anastomosis is considered after resection of the jejunum for gastrojejunal ulcer, it should be placed proximal to the gastro-anastomosis.

It is our opinion that infection plays only a secondary rôle, and that unabsorbable material, clamps and hematoma are only casually responsible for the formation of postoperative peptic ulcer.

## EXPERIMENTAL ILEUS

### II. HIGH OBSTRUCTION WITH THE BILIARY, PANCREATIC AND DUODENAL SECRETIONS, ALONG WITH FOOD AND SODIUM CHLORIDE ENTERING THE BOWEL BELOW THE OBSTRUCTED POINT

HILGER PERRY JENKINS, M.D.

CHICAGO

In a previous communication<sup>1</sup> high obstruction in the dog was found to be compatible with life as long as a month if the biliary, pancreatic and duodenal secretions were short-circuited below the point of obstruction. Six animals lived from twelve to thirty-three days, drank water and ate food occasionally, vomited from time to time, lost weight gradually and showed a gradual fall in blood chlorides and a rise in carbon dioxide-combining power and nonprotein nitrogen, which was most marked shortly before death.

This experiment has been modified in the following manner: The biliary, pancreatic and duodenal secretions were short-circuited by the same type of procedures as described in the previous paper, but in addition the bowel below the point of obstruction was brought out through the abdominal wall as a jejunostomy. Through this the animal was fed milk and cream with small amounts of sodium chloride added and in some instances other substances.

#### EXPERIMENT

*Technic.*—The dogs were prepared for obstruction by one or two preliminary operations. Morphine-ether anesthesia was used. Most of the animals were operated on in the following sequence: At the first stage an entero-enterostomy was made between the jejunum just beyond the ligament of Treitz and the jejunum 2 or 3 feet (from 60 to 90 cm.) lower down. At the second stage a pylorectomy and anterior gastro-enterostomy were performed, the jejunum just beyond the entero-enterostomy being used. At the third stage the obstruction was produced in the jejunum just above the entero-enterostomy, and the jejunum was sectioned between the entero-enterostomy and the gastro-enterostomy. The distal stump of jejunum just beyond the obstruction and proximal to the entero-enterostomy was brought to the outside as a jejunostomy. (Figure 1 shows a diagram of the operative procedures.) As a result of these procedures the stomach emptied into

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From the Department of Surgery, the University of Chicago.

1. Jenkins, H. P.: Experimental Ileus: I. High Obstruction with the Biliary, Pancreatic and Duodenal Secretions Short-Circuited Below the Obstructed Point. Arch. Surg. 19:1072 (Dec.) 1929.

the short obstructed loop of jejunum, and the biliary, pancreatic and duodenal secretions as well as food and fluids introduced through the jejunostomy emptied into the bowel below the obstruction.

In several dogs the operative procedures were cut down to two stages. Forced feedings of milk and table scraps in addition to the regular kennel diet were necessary to bring the weights of the animals back to normal after the preliminary operations. Animals that did not regain their original weight were discarded. The animals were kept in metabolism cages. During the period of obstruction the weights were recorded daily. Blood was taken for chemical examination about once a week or oftener if the condition of the animal appeared to show marked change. The plasma carbon dioxide-combining power was determined in volumes per hundred cubic centimeters by the Van Slyke method. The total whole blood chlorides were estimated as sodium chloride by Whitehorn's modification of Volhard's technic. The nonprotein nitrogen was determined by Koch and McMeekin's method.

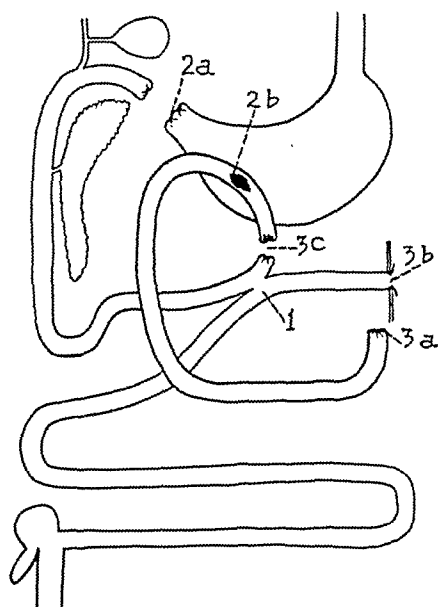


Fig. 1.—Diagram of operative procedures: 1, entero-enterostomy; 2a, pylorectomy; 2b, anterior gastro-enterostomy; 3a, obstruction; 3b, jejunostomy, and 3c, section of jejunum.

The technic of feeding consisted of introducing milk and cream to which an egg was sometimes added into the opening created by the jejunostomy through a catheter connected with a funnel. In some instances other substances were added. The animals appeared to get along better when small amounts were given frequently than when large amounts were given less often. Following the feeding there would frequently be regurgitation of food and digestive secretions from the jejunostomy. This was controlled by inserting a plug into the opening of the bowel. This plug was made by packing a small wad of cotton into the tip of a rubber glove finger. This was fastened to a piece of rolled gauze on the outside which prevented it from slipping down into the bowel farther than the inner side of the abdominal wall. Without this type of plug there was loss of food and also marked digestion of the skin about the jejunostomy from the digestive secretions.

## PROTOCOLS

SERIES I.—Six dogs operated on first (see Series II), that lived from four to twelve days.

*Dog 19.*—The weight at the time of obstruction and jejunostomy was 30 Kg. On the first day the jejunostomy was opened, and 1,000 cc. of milk, 50 Gm. of dextrose and 10 Gm. of sodium chloride were given through the jejunostomy in two feedings. This was repeated on the second and third days. Marked diarrhea developed on the third day. The animal became very weak and died on the fourth day. The autopsy revealed no complications. The obstructed part of the jejunum measured 90 cm. and showed no noticeable distention.

*Dog 83.*—The original weight at the time of the obstruction and jejunostomy was 11.2 Kg. On the first day, 250 cc. of milk and cream with two eggs was given. On the following three days 450 cc. of milk and cream with three eggs was given. On the fourth day 2 Gm. of sodium chloride was added to the feedings. Vomiting occurred at least four times. The animal was found dead on the fifth day. At autopsy there was no evidence of complications, and the 23 cm. of obstructed jejunum showed no distention.

TABLE 1.—Results of Chemical Examination of the Blood of Animals of Series I

Dog	Day	Chlorides	Nonprotein Nitrogen	Carbon Dioxide
872.....	0	534	36	48
	7	621	31	55
	8	Death		
86.....	0	424	28	53
	7	509	221	?
	7	Death		
918.....	0	534	38	43
	10	540	37	?
	11	Death		
942.....	0	522	23	49
	7	603	26	50
	12	Death		

*Dog 872.*—When the obstruction and jejunostomy were done, the weight was 11.7 Kg. The animal was given feedings of from 500 to 1,000 cc. of milk with small amounts of sodium chloride daily. The results of chemical examination of the blood on the seventh day were practically the same as before operation (table 1 shows the results for series I). Death occurred on the eighth day. The autopsy revealed no complications. There was no distention of the 55 cm. of obstructed jejunum.

*Dog 86.*—The animal weighed 13 Kg. when the obstruction was produced and the jejunostomy performed. The feedings consisted of from 300 to 500 cc. of milk and cream daily. On the first two days 3 Gm. of sodium chloride was added daily. A bloody diarrhea developed on the fourth day and continued until death occurred on the seventh day. Chemical examination of the blood just before death showed high nonprotein nitrogen and a slight rise in the blood chlorides from 424 to 509 mg. per hundred cubic centimeters. Autopsy revealed no point of hemorrhage in the bowel. The obstructed portion of the bowel was not distended. It measured 25 cm. in length. It was impossible to determine whether the hemorrhage from the bowel was much of a factor in the cause of death. There was no gross evidence of complication.

*Dog 918.*—The animal weighed 23.2 Kg. when the obstruction was produced and the jejunostomy performed. From the second day, from 750 to 1,000 cc. of fluids, consisting of physiologic solution of sodium chloride, milk and dextrose, was given daily in two feedings. Chemical examination of the blood on the tenth day showed practically no change in the chlorides or nonprotein nitrogen. The dog died on the eleventh day, and the postmortem examination showed marked bronchopneumonia, general peritonitis from gangrene and perforation of the loop of bowel brought to the outside as a jejunostomy. The obstructed portion of the bowel measured 40 cm. and was not distended.

*Dog 942.*—When the obstruction was produced and the jejunostomy performed the dog weighed 13 Kg. The daily feedings of 250 cc. of milk and cream with 2 Gm. of sodium chloride were tolerated poorly, because the animal vomited after most of the feedings. Sometimes material that had been put into the opening produced by jejunostomy was vomited. Chemical examination of the blood made on the seventh day showed little change except a slight rise in chlorides. Death occurred on the twelfth day, and at autopsy there was no evidence of a complication. There was, however, reestablishment of a very small lumen of the sectioned jejunum proximal to the site of the gastro-enterostomy. This explained why some of the material injected into the jejunostomy opening appeared in the vomitus. There was no distention of the obstructed portion of the bowel. It is difficult to ascertain whether the reestablishment of a small lumen would appreciably alter the results in this animal. Nevertheless the data on this dog must be considered as possibly atypical even though they fit in with the results that were obtained in the other animals of the series.

*SERIES II.—Five dogs that lived from twenty-one to thirty-seven days.*

*Dog 96.*—During the first week after obstruction and jejunostomy about 500 cc. of 2 per cent sodium chloride was given daily by mouth and practically nothing through the jejunostomy opening. Then the diet consisted of 750 cc. of milk and cream and two eggs given in three feedings daily through the opening. In addition, during the second week, only about 250 cc. of water was given by mouth daily. During the third week 5 Gm. of sodium chloride was given daily with the feedings. Vomiting occurred about three times a week. The animal passed two or three very soft stools daily. The weight gradually declined from 18 Kg. to 11.4 Kg. on the twenty-third day, when the dog died. Chemical examination of the blood showed a moderate rise in chlorides from 520 to 640 mg. per hundred cubic centimeters, and only slight fluctuation in the carbon dioxide and nonprotein nitrogen. (Figure 2 shows weight and readings made on chemical examination of the blood.) Autopsy showed no evidence of complication. The obstructed portion of the bowel was 67 cm. long and was not distended.

*Dog 88.*—During the first ten days following the obstruction and jejunostomy the feedings consisted of 250 cc. of milk and cream, one egg and 1 Gm. of sodium chloride given three times a day. During the following days the amount of milk and cream was cut down to 100 cc. given seven times a day. Occasionally an egg was added but no sodium chloride. The weight declined from 19 to 13.7 Kg. Vomiting occurred on at least eight days. About two soft stools were passed daily. The animal died on the twenty-first day without any apparent sign of terminal weakness. Chemical examination of the blood showed a slight rise in chlorides from 443 to 510 mg. per hundred cubic centimeters. The nonprotein nitrogen rose to the high figure of 115 mg. per hundred cubic centimeters on the day of death, and the carbon dioxide dropped from 61 mg. before operation to 24 mg. on the last day (figure 3 shows the weight and the results of the chemical examination).

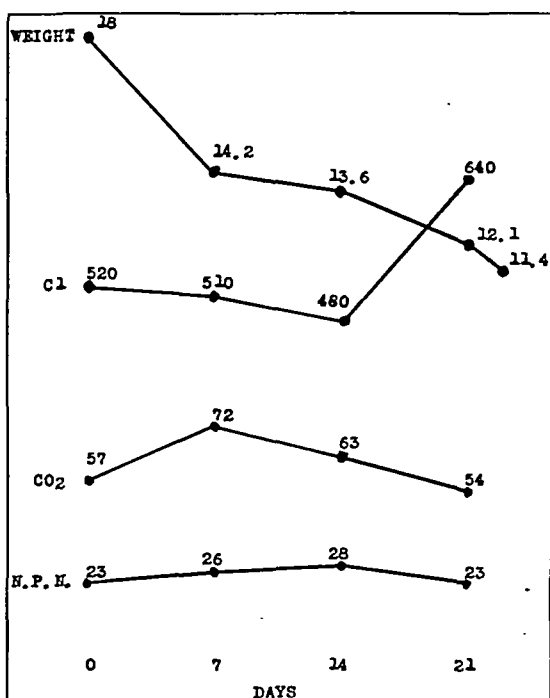


Fig. 2.—Weight and results of chemical examination of the blood of dog 96; death occurred on the twenty-third day..

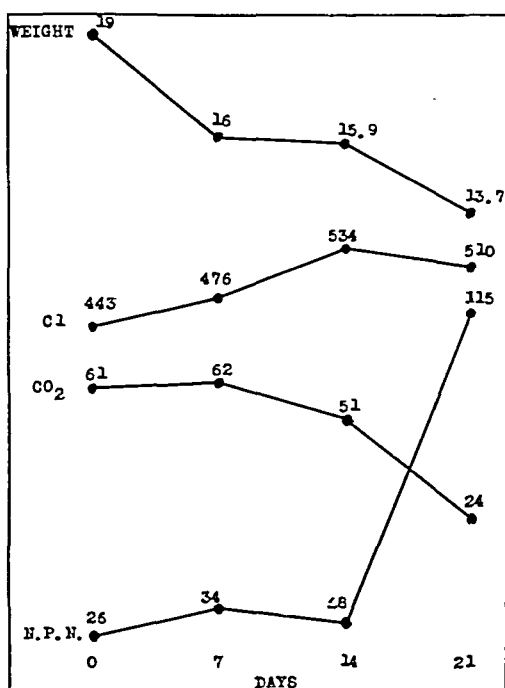


Fig. 3.—Weight and results of chemical examination of the blood of dog 88; death occurred on the twenty-first day.



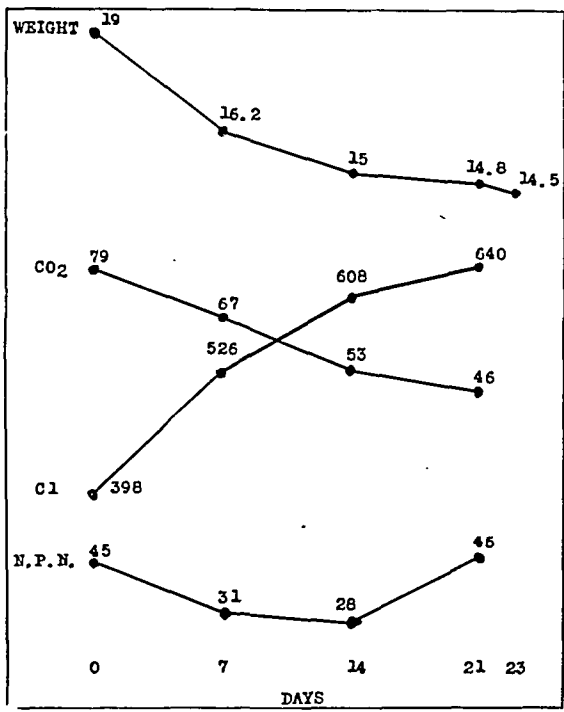


Fig. 4.—Weight and results of chemical examination of the blood of dog 945: death occurred on the twenty-third day.

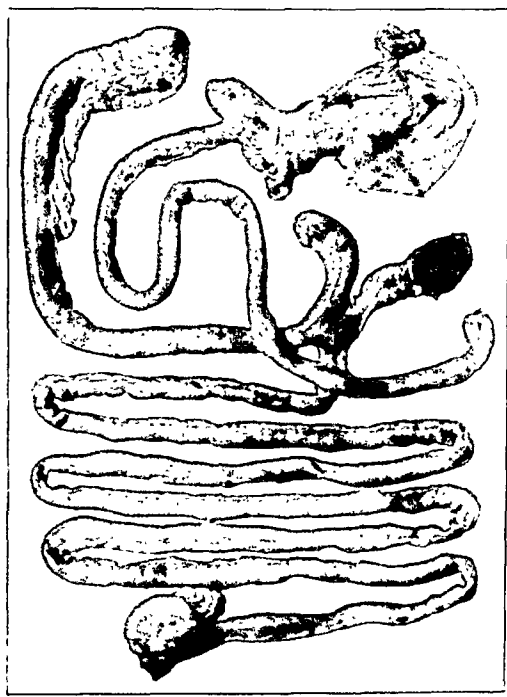


Fig. 5.—Specimen from dog 945; the obstructed portion of the jejunum measured 65 cm.; death occurred on the twenty-third day.

Autopsy revealed marked bronchopneumonia. The obstructed portion of the bowel was 72 cm. long and showed no evidence of distention.

*Dog 945.*—The feedings were given three times a day for the first eleven days following the obstruction and jejunostomy as was done in the case of dog 88, and then seven times a day. The weight declined from 19 Kg. to 14.5 Kg. on the twenty-third day, when death occurred without any premonitory sign. The stools were practically of the same type as those reported for dog 88. Chemical examination of the blood up to the end of the third week showed a rise in chlorides from 398 mg. per hundred cubic centimeters before operation to 640 mg. two days before death. The carbon dioxide, which was originally somewhat higher than normal, dropped from 79 to 46 mg. The nonprotein nitrogen was originally 45 mg. and after a slight fall rose to 46 mg. (Figure 4 shows weight and results of chemical examination.) Autopsy showed only a small patch of bronchopneumonia. There was no evidence of a complication other than this. The obstructed portion of the bowel measured 65 cm. and was not distended. (Figure 5 shows the specimen.) The patch of pneumonia did not appear to be sufficiently extensive to explain completely the cause of death.

*Dog 919.*—During the first nine days following the obstruction and jejunostomy feedings were given three times a day and from then on seven times a day, as described for dog 88. No sodium chloride was given after the ninth day. The stools averaged two a day. Vomiting occurred at least ten times. The weight declined from 16 Kg. to 9.6 Kg. on the thirty-second day, when death occurred. During the last four days the animal became progressively weaker. Chemical examination of the blood up to the thirty-first day showed a very slight fall in chlorides from 492 to 460 mg. per hundred cubic centimeters, a rise in carbon dioxide from 52 to 71 mg. and a fall in nonprotein nitrogen from 33 to 27 mg. (Figure 6 shows weight and results of chemical examination.) At autopsy an extensive cervical cellulitis and mediastinitis were found, which were probably the result of the drawing of blood from the jugular vein. In addition there were an extensive bronchopneumonia and areas of necrosis and ulceration in the esophagus. The stomach was markedly dilated, but the obstructed portion of the jejunum was only slightly distended. (Figure 7 shows the specimen.) This portion of the jejunum measured 48 cm. in length. Gross blood was found in the stools the day before death, but no apparent source of the bleeding was found at necropsy.

*Dog 134.*—The feedings were 150 cc. of milk and cream given seven times a day for the first three weeks following the obstruction. Then 100 cc. was given ten times a day. About 15 cc. of pure gastric juice was added to each feeding from the eighteenth to the twenty-eighth day. The gastric juice was obtained from one of Dragstedt's<sup>2</sup> dogs which had a complete isolated pouch of the stomach. On the eighteenth day the gastric analysis of the obstructed animal showed a free acidity of 19 points and a total acidity of 81. On the thirty-fifth day there was no free acid present, but the combined acid was 68. The blood count on the twenty-eighth day was 70 per cent hemoglobin, 5,080,000 red blood cells and 7,000 white blood cells. On the thirty-fifth day the hemoglobin was also 70 per cent, but the red cells were 4,160,000 and the white cells were 8,400. Vomiting occurred about two or three times a week. Two or three stools were passed daily. These were soft and sometimes formed, but never watery. The weight slowly declined from 19.6 Kg. to 13.7 Kg. on the thirty-seventh day. Chemical examination of the blood showed relatively little change during the first five weeks, but on the day of death

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2. Dragstedt, L. R., and Ellis, J. C.: The Fatal Effect of the Total Loss of Gastric Juice, *Am. J. Physiol.* **93**:407 (June) 1930.

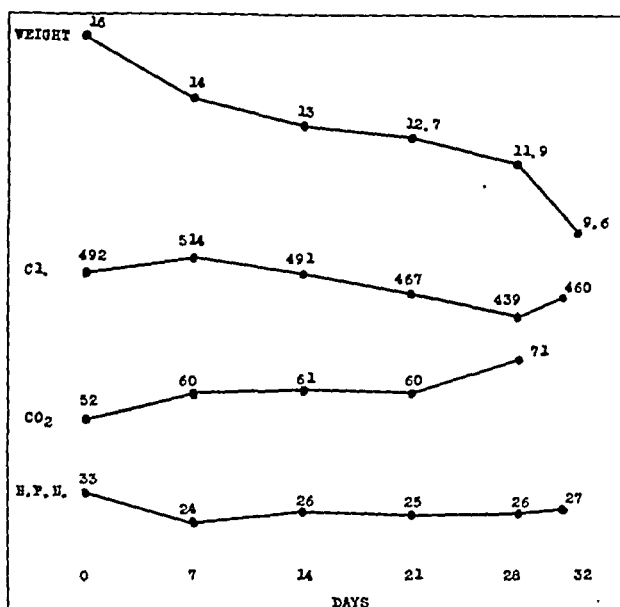


Fig. 6.—Weight and results of chemical examination of the blood of dog 919; death occurred on the thirty-second day.



Fig. 7.—Specimen from dog 919, showing slight distention of the obstructed segment of jejunum, which measured 48 cm.; death occurred on the thirty-second day.

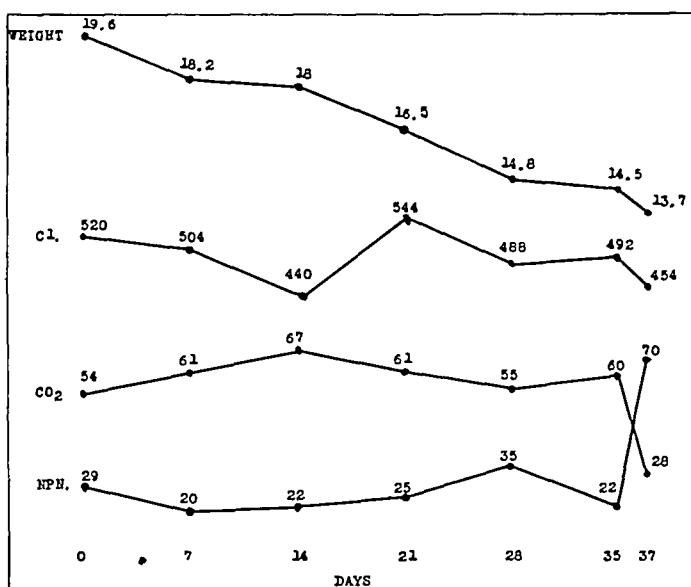


Fig. 8.—Weight and results of chemical examination of the blood of dog 134; death occurred on the thirty-seventh day.

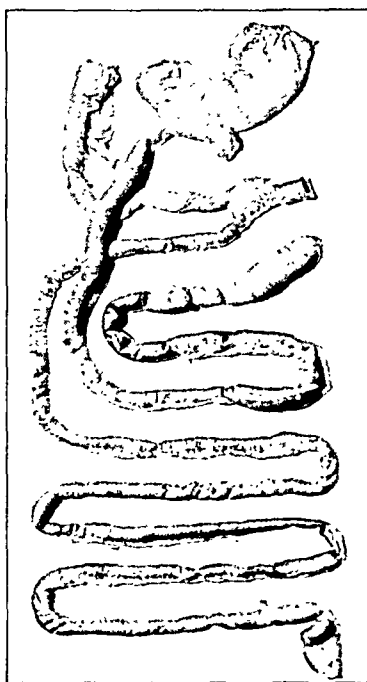


Fig. 9.—Specimen from dog 134, showing slight distention of the obstructed segment of jejunum, which measured 80 cm.; death occurred on the thirty-seventh day.

the carbon dioxide dropped to 27 mg. per hundred cubic centimeters, and the non-protein nitrogen rose to 70 mg.; however, the chlorides were only slightly lower than the original figure of 520 mg., dropping to 454 mg. (Figure 8 shows the weight and chemical readings.) During the last two days the animal became progressively weaker until death occurred on the thirty-seventh day. Autopsy revealed no evidence of a complication. The obstructed portion of the bowel was 80 cm. long and was slightly distended, especially at the distal end (figure 9 shows the specimen).

#### COMMENT

The cause of death in intestinal obstruction has been attributed by most clinicians and investigators to toxemia. The nature of this toxemia has not been definitely established. Recently some investigators<sup>3</sup> have drawn attention to a difference between simple high obstruction in which vomiting is a conspicuous feature and obstruction with damage to the blood supply of the bowel by distention or strangulation. They believe that death is due to toxemia in the latter, whereas in the former the lethal outcome is brought about by the loss of digestive secretions alone.

The interpretation of the results of this experiment is not altogether clear. The marked variability in length of life of the animals with intestinal obstruction, all treated in practically the same manner, can not be satisfactorily explained. However, there are several points that may be considered in comparing the two groups. In the first series, which survived only from four to twelve days, the animals were given large feedings two or three times a day, vomiting occurred frequently, especially after feeding, and diarrhea was often present. There was no distention of the obstructed portion of the bowel at autopsy, and chemical examination of the blood showed a slight rise in chlorides. In the second series, which lived from three to five weeks, the nursing was better, the feedings were given more frequently and in smaller amounts at least part of the time, the dogs were larger with one exception, vomiting occurred less frequently and seldom following or during a feeding, and diarrhea was not present.

In comparing this experiment with that described in the previous communication,<sup>1</sup> the only outstanding difference in the way the animals were treated was in the addition of food and sodium chloride below the obstruction. Although, from no apparent cause other than the obstruction, some of the animals died much sooner than those that received

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3. Gatch, W. D.: Trussler, H. M., and Ayres, K. D.: Causes of Death in Acute Intestinal Obstruction, *Surg., Gynec. & Obst.* **46**:332 (March) 1928. McIver, M. A., and Gamble, J. L.: Body Fluid Changes Due to Upper Intestinal Obstruction, *J. A. M. A.* **91**:1589 (Nov. 24) 1928. White, J. C., and Fender, F. A.: The Cause of Death in Uncomplicated High Intestinal Obstruction, *Arch. Surg.* **20**:897 (June) 1930. Morton, J. J., and Pearse, H. E.: The Similarity in Effect of Experimental High Intestinal Obstruction and High Complete Intestinal Fistula, *Ann. Surg.* **94**:263 (Aug.) 1931.

no food, one animal was kept alive longer with the feedings than any of the animals in the previous experiment. The changes in the chemical constituents of the blood were rather marked in the series of animals referred to in the previous report; that is, there were a fall in chlorides and a rise in carbon dioxide and in nonprotein nitrogen. However, in this experiment there was not a single instance of a marked fall in chlorides. The most noticeable fall in chlorides was from 520 to 454 mg. per hundred cubic centimeters in dog 134, which lived thirty-seven days. In the animal that lived thirty-two days there was only a slight fall from 492 to 460 mg. In all the others there was a rise in chlorides. The nonprotein nitrogen was more inclined to show a rise than a fall, and the carbon dioxide showed more of a tendency to fall than to rise. However, the changes were seldom marked for either.

The fall that was observed in the blood chlorides in the previous experiment<sup>1</sup> could be accounted for on the basis of loss of gastric juice as observed in simple pyloric obstruction<sup>4</sup> or as shown by Dragstedt<sup>2</sup> in complete isolated pouches of the stomach. However, the presence of a short loop of jejunum offered opportunity for resorption of enough of the gastric juice to prevent the rapidly fatal outcome of complete loss of gastric juice that occurs in pyloric obstruction or in complete pouches of the stomach. In this experiment, in addition to the short loop of jejunum which permitted some resorption of gastric juice, there was opportunity below the obstruction for absorption of sodium chloride in the milk itself or added to the milk, and in one instance of gastric juice, which replaced the chlorides that had been lost in the vomitus. This would probably account for the maintenance of the blood chlorides at a fairly high level during the period of obstruction.

Milk contains approximately 0.13 per cent of sodium chloride.<sup>5</sup> In several animals there was a considerable period when sodium chloride was not added to the feedings, and the maintenance of the blood chlorides at a fairly high level during these periods was apparently due to the sodium chloride in the milk. In dog 134 no sodium chloride was added to the feedings. At the end of two weeks the blood chlorides had fallen only from 520 to 440 mg. per hundred cubic centimeters; the latter figure was considerably higher than that for the blood chlorides at the end of two weeks in any of the animals of the previous experiment. However, when the gastric juice was added to the feedings from the eighteenth to the twenty-eighth day, there was a moderate rise in blood chlorides during that period. In dog 919 sodium

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4. Hastings, A. B.; Murray, C. D., and Murray, H. A.: Certain Chemical Changes in the Blood After Pyloric Obstruction in Dogs, *J. Biol. Chem.* **46**:223, 1921.

5. Van Slyke, L. L., and Bosworth, A. B.: Condition of Casein and Salts in Milk, *J. Biol. Chem.* **20**:135, 1915.

chloride was added only during the first nine days. From then on the sodium chloride in the milk was apparently adequate to keep the blood chlorides fairly high during the rest of the thirty-two days of obstruction. In dogs 88 and 945 sodium chloride was added only during the first half of the period of obstruction; however, the blood chlorides showed no tendency to fall.

The diet in this experiment was calculated to contain more calories than would be necessary for maintenance; however, all the animals lost weight. The animal that lived thirty-seven days lost 5.9 Kg. This was an average of 0.16 Kg. per day, as compared with the daily loss of 0.32 Kg. per day in the animal that lived thirty-three days in the previously reported experiment without feedings. This would tend to show that while starvation may influence the length of life in obstruction it was not the determining factor in the cause of death, at least in this experiment.

The results of an experiment similar to this one have been recently published by Pearse.<sup>6</sup> In addition to short-circuiting the biliary, pancreatic and duodenal secretions below the obstruction, the pyloric part of the stomach was also drained below the obstruction, while the fundus drained into the obstructed segment of jejunum. Gastrostomy was performed in the pyloric section of the stomach, and milk was administered, together with some sodium chloride. Some of the animals were kept alive a month in this manner; then they were killed. There was no more evidence of toxemia in these animals than was observed in the dogs described in this paper. The blood showed only a slight tendency to decrease in chlorides, and as soon as a fall occurred the administration of sodium chloride into the bowel would bring the chlorides back to a higher level.

#### SUMMARY

1. When high intestinal obstruction was produced in dogs with the biliary, pancreatic and duodenal secretions short-circuited below the point of obstruction and the animals fed milk and cream, with sodium chloride sometimes added, through a jejunostomy opening below the obstruction, some animals lived from three to five weeks, while others did not survive longer than from four to twelve days. (Table 2 gives the length of life, the weight and the length of the obstructed portion of the bowel.)

2. The animals usually remained in fairly good condition until shortly before death.

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6. Pearse, H. E.: Is Toxaemia the Cause of Death in Uncomplicated Intestinal Obstruction? *Ann. Surg.* 93:915 (April) 1931.

3. Vomiting throughout the period of obstruction was a conspicuous feature in some animals, while in others it did not occur oftener than three times a week.

4. The weight showed a gradual decline in spite of the high caloric value of the food taken. The loss of weight was less marked when the feedings were frequent and small.

5. Chemical studies of the blood showed no marked fall in chlorides. In two instances there was a slight fall, but the amount of chlorides was still within the range of normal, while all the other animals showed a rise. The carbon dioxide and nonprotein nitrogen showed no marked constant changes.

6. In the first series of six animals which lived from four to twelve days, autopsy revealed in only one animal evidence of a complication

TABLE 2.—*Length of Life, Weight and Length of Obstructed Bowel*

	Dog	Length of Life (Days)	Weight (Kg.)	Obstructed Bowel (Cm.)
Series I.....	19	4	30.0	90
	83	5	11.2	23
	872	8	11.7	55
	86	7	13.0	25
	918	11	23.2	40
	942	12	13.0	35
Series II.....	96	23	18.0	67
	88	21	19.0	72
	945	23	19.0	65
	919	32	16.0	48
	134	37	19.6	80

that would explain death as due to any other factor than the presence of an obstruction. In the second series of five dogs which survived from three to five weeks, death was definitely due to a complication in two animals and possibly in three. There was no appreciable distention of the obstructed portion of the bowel except in the two animals that lived thirty-two and thirty-seven days.

#### CONCLUSIONS

1. The variability of the length of life of the animals with high intestinal obstruction in these experiments cannot be easily explained by either the toxic theory or that of the loss of digestive secretions.

2. The prolonged life of the animals in the second series that lived from three to five weeks, however, does appear to fit in with the theory of loss of digestive secretions.<sup>7</sup> This increased length of life compared with that of animals with simple obstruction at approximately the same

7. Dragstedt, L. R.: Failure of Reabsorption of Gastric and Pancreatic Juice, *Am. J. Surg.* **11**:544 (March) 1931.



level may possibly be due to the resorption of the biliary, pancreatic and duodenal secretions below the point of obstruction, along with some resorption of gastric juice in the obstructed segment of jejunum. It also appears that the maintenance of the blood chlorides at a fairly high level during the period of obstruction as compared with the fall in chlorides observed in the previous experiment<sup>1</sup> was due to the replacement of chlorides lost in the vomited gastric juice by the sodium chloride present in the milk, as well as by that which was added to it, and in one instance by gastric juice.

3. Nevertheless this does not explain why the animals in the first series except in one instance died in from four to twelve days without a fall in chlorides, without distention of the obstructed bowel and without any other apparent cause than the presence of an obstruction. Furthermore, it would be difficult to explain the death of the animals in this series on the basis of toxemia when there was practically no distention of the obstructed portion of the bowel.

# WHITMAN RECONSTRUCTION OPERATION ON THE HIP JOINT

AN ANALYSIS OF LATE RESULTS

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In 1921, Whitman<sup>1</sup> reported an operative procedure for ununited fracture of the neck of the femur which resulted in a stable, painless hip with satisfactory motion. This differed widely from bone pegging and the Brackett operations inasmuch as the femoral head was removed, the femoral neck placed into the acetabulum and the greater trochanter transplanted downward on the shaft. Four years later, Rechtman<sup>2</sup> reported thirty-four cases from Whitman's service in which this operation had been performed. He broadened the indications to cover not only nonunion of fracture of the neck of the femur but also to include malum coxae senilis, quiescent tuberculous hip, acute epiphysitis and Charcot hip. In 1926, Armitage Whitman<sup>3</sup> presented the late results in nine cases. His patients had an average motion of 45 degrees flexion and 10 degrees abduction. Four of these patients used a cane. All had diminished pain following the intervention. In the orthopedic department of the State University of Iowa, eighteen patients have had the Whitman reconstruction operation performed for ununited fracture of the neck of the femur and for arthritides of the hip. This report represents an analysis of the final results.

## INDICATIONS

The Whitman reconstruction operation was devised to correct the deformity and to produce a stable joint that allows motion without pain. We therefore believe that the operation is applicable primarily, of course, in ununited fracture of the neck of the femur and, secondarily, in a pathologic dislocation of the hip, in old slipped femoral epiphyses

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From the Department of Orthopedic Surgery, State University of Iowa, Iowa City.

1. Whitman, Royal: The Reconstruction Operation for Ununited Fracture of the Neck of the Femur, *Surg., Gynec. & Obst.* **32:6** (June) 1921.

2. Rechtman, A. M.: The Reconstruction Operation on the Hip, *Arch. Surg.* **11:842** (Dec.) 1925.

3. Whitman, Armitage: Remarks Preparatory to a Cinematographic Presentation of Late Results of the Reconstruction Operation, *J. Bone & Joint Surg.* **8:803** (Oct.) 1926.

and in osteo-arthritis or traumatic arthritis of the hip. In these conditions, pain, instability, loss of motion and deformity are the complaints. The Whitman reconstruction is suitable for meeting all of these symptoms.

#### CONTRAINDICATIONS AND COMPLICATIONS

Because of the attending dangers and the possibility of complications, the operation cannot be carried out in all cases which present the foregoing symptoms. It is indicated only in good surgical risks. Age is an important factor. In the series of eighteen cases from the orthopedic department the average age was 46, the oldest patient being 63 and the youngest 16.

The operation is contraindicated in tuberculosis and arthropathy. Rechtman<sup>2</sup> reported the cases of two patients with quiescent tuberculous hips who developed sinuses following the operations. In our one case with Charcot hip in which the Whitman reconstruction method was used, there was postoperative acetabular destruction resulting in complete failure.

Of complications, embolism is prominently mentioned in the literature. Among seventy-four cases reported, three patients died of emboli, two had emboli but recovered and one died of shock. Other operative complications are shock and bronchopneumonia. The immediate post-operative complications encountered in our series, in spite of careful selection of cases and rigid adherence to restrictions in indications, are as follows:

Uneventful .....	7
Slight shock .....	2
Moderate shock .....	3
Severe shock .....	2
Bronchopneumonia .....	1
Death .....	1
No data available .....	2

#### PROCEDURE

The Whitman reconstruction operation is based on three principal steps: first, the removal of the head; second, the insertion of the remaining neck or of the end of the shaft of the femur into the vacated acetabulum, and third, the transplantation of the greater trochanter with its muscular attachments downward on the shaft spine of the ilium of the femur.

The joint is approached by a J-shaped incision running longitudinally downward from the anterior superior spine of the ilium to below the base of the greater trochanter, and then backward, crossing the trochanteric region. The greater trochanter is chiseled off at its base along a line parallel to the long axis of the femoral neck. Its muscular attachments are left intact as it is retracted upwardly and laterally. After opening the capsule, the head is removed and the end of the neck smoothed off. The neck is then inserted deep into the acetabulum, with the shaft of the femur in 150 degrees abduction. While the extremity is held so, a bed

is prepared on the outer side of the shaft to receive the greater trochanter. The trochanter is then pulled down to its new bed and fastened by means of nails or heavy drillhole sutures.

A double hip spica is applied in abduction, extension and neutral rotatory position. The patient remains in bed in this cast for approximately from four to six weeks. He then is allowed up on crutches, still wearing a cast. Physical therapy is instituted from six to ten weeks after operation, according to the degree of fusion of the trochanter to the shaft, as seen in the x-ray picture.

#### ANALYSIS OF FINAL RESULTS

*Length of Observation.*—Since 1926, when the first operation was performed in this clinic, eighteen patients have had a Whitman reconstruction operation. Of these eighteen, three patients could not be traced; the remaining fifteen have been checked up personally, except a few whose condition was ascertained by questionnaire. Dr. Steindler



Fig. 1.—Whitman reconstruction for ununited fracture of the neck of the femur. Two nails fastened the trochanter to the shaft. The patient had a good result.

operated on thirteen of these patients, and older members of his staff on the others, all using the foregoing technic. The average length of personal observation following operation has been twenty months, the longest four years and the shortest two months. Patients continue to improve and develop more motion for a year and a half; after this their condition remains practically stationary. No signs of arthritis developed in any of the cases.

*Shortening.*—In his first paper, Whitman remarked that occasionally the operation diminishes the preexisting shortening. One of our patients gained  $\frac{1}{4}$  inch (0.63 cm.) in length as a result of the operation. On the other hand, another patient lost  $3\frac{3}{4}$  inches (9.5 cm.) after the operation. The average change in length that could be attributed to the operation was 1 inch (2.5 cm.) shortening. However, mobility, favorable position and stability render this loss comparatively insignificant.

*Mobility.*—This operation was designed primarily to correct a deformity and produce a stable, painless hip. Whitman believed, at first, that motion was a secondary consideration. Since the operation is in reality an arthroplasty, we consider mobility an essential attribute of a good result. Commonly a flexion contracture occurs, but this is usually slight enough to be of no importance. This flexion contracture amounted in fourteen patients to an average of 14 degrees. The average free range of flexion was 67 degrees. Contractures did not occur



Fig. 2.—The arrow points to a compression fracture of the femoral head. After operation the patient was free from pain; the hip was movable and stable, and good result was obtained.



Fig. 3.—Charcot hip. *A*, before operation this was apparently an ordinary ununited fracture of the neck of the femur. *B*, after operation, the acetabulum disintegrated and the femur dislocated. Failure resulted.

in other than the sagittal plane of motion. Approximately 20 degrees adduction and 20 degrees abduction could be obtained. Internal rotation was usually limited. Such a degree of mobility in previously stiff or unstable joints was certainly satisfactory.

*Stability.*—One of the chief advantages of the reconstruction operation is a stable hip. With a smoothly rounded neck or end of the femoral shaft placed well in the acetabulum, as verified by postoperative x-ray pictures, stability is assured. From examination of fifteen

patients, fourteen were found to have a stable, weight-bearing joint (see table). Two of these fourteen even had a negative Trendelenburg sign. Eight of the fourteen needed no external support whatever. Four of these fourteen used some support for reasons other than inability to bear weight on the hip, e. g., two because of general osteoarthritis, and one because of a posttyphoid transverse myelitis; one wore artificial limbs, both his legs having been amputated. The fifteenth patient had a Charcot hip. His acetabulum disintegrated; the joint telescoped and became unstable.

*Painlessness.*—Pain was the prime reason that caused the patients with ununited fracture of the neck of the femur or arthritis of the hip to seek aid by operation. The relief from pain is the main contribution of the reconstruction operation in these cases. All of the fourteen

#### *Late Postoperative Findings*

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1. Pain	
None .....	12
Slight discomfort .....	2
No data available.....	4
2. Stability	
Excellent (negative Trendelenburg sign).....	2
Good (no support but positive Trendelenburg).....	8
Stable (using support for extrinsic reasons).....	4
Poor (telescoping) .....	1
No data available.....	3
3. Average range of motion	
Flexion 166-99 degrees = 67 degrees	
Abduction 150-158 degrees = 22 degrees	
Adduction 180-161 degrees = 19 degrees	
Internal rotation = 8 degrees	
External rotation = 26 degrees	

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patients on whom data were secured in regard to this point were improved. Twelve patients had painless hips (see table). One patient had some discomfort. He had had a traumatic fracture dislocation, and the head was very difficult to remove. Roentgenograms showed that a small portion of the head had been left behind. Another patient had some discomfort for unknown reasons, but two observers who examined this patient separately noted that she had improved greatly.

#### END-RESULTS

Only when pain, shortening, stability and mobility are considered together, may the final result of the Whitman reconstruction operation be ascertained. Among the fifteen patients on whom we have these late findings, eight had had an ununited fracture of the neck of the femur; two, osteo-arthritis of the hip; two, suppurative arthritis; one, generalized atrophic arthritis; one, traumatic dislocated hip and one, Charcot hip. Of these fifteen patients, eleven had good results. The

result was good in all (eight) cases of ununited fracture of the neck of the femur. The end results in the eighteen cases are as follows:

Good .....	11
Fair .....	3
Failure .....	1
No late findings .....	3

#### ANALYSIS OF POORER RESULTS

The good results need no further discussion. However, further consideration should be given to the other four cases. Among them is a patient with a destructive arthritis of the hip. The femoral head, in her case, had to be chiseled from the acetabulum. After one and a half years of observation she has a painless, stable but ankylosed hip. She walks with only a slight limp. Because of the lack of motion this case is classified as a fair result. Another patient had bilateral suppurative arthritis of both hips with bony fusion of one and a partially destroyed and unstable joint on the other. A reconstruction was done on the latter with very little benefit. Although the patient has a painless hip with a negative Trendelenburg sign, yet the ranges of motion of the hip on which the operation was performed are so limited that, with the other joint fused, he has to use crutches when walking any moderate distance. Whether an arthroplasty of the opposite hip would provide a better result for the reconstruction is a matter of conjecture. This result as it now appears is only fair. A third patient had generalized arthritis with a partially ankylosed and painful hip. After the first operation the greater trochanter failed to fuse with the shaft, and the neck of the femur dislocated, so that a year later another operation was performed. Now, four years after the last operation, she has a painless, stable, movable joint, but there is a shortening of 4 inches (10.16 cm.). Because of the great inequality of length of the extremities, this is considered only a fair result. Another patient had an ununited fracture of the neck of the femur. He had a positive Wassermann reaction, and was given antisyphilitic therapy before operation. Immediately following the operation the acetabulum rapidly disintegrated, and loose bony masses formed about the hip. Definite tabetic symptoms became evident for the first time. The diagnosis was changed to Charcot hip. With the loss of the acetabular roof, the femur dislocated, giving the patient a useless hip. This case is the only complete failure in this series.

#### SUMMARY

An analysis of the end-results of fifteen cases in which a Whitman reconstruction operation was performed has been made. This operation is indicated in ununited fracture of the neck of the femur and arthri-

tides of the hip to alleviate pain, deformity, instability and to allow useful ranges of motion. The operation carries a moderate surgical risk. All patients who were operated on because of ununited fracture of the neck of the femur showed a good result. The final outcome is less certain in patients with arthritic lesions; yet the results obtained were satisfactory enough to make the operation advisable also in this group of cases.



# CHANGES IN THE SYMPHYSIS PUBIS AND SACRO-ILIAC ARTICULATIONS AS A RESULT OF PREGNANCY AND CHILDBIRTH

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AND

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For a certain length of time the idea existed that during labor the entire pelvic ring is incapable of any change in size. Clinical observations, however, support the assumption that during pregnancy and labor not only is a certain amount of movement possible in the pelvic joints, but a distinct stretching or widening takes place. Some of these observations are directly confirmable; others can be made during actual labor.

The normal articular cavities of the symphysis pubis and the sacro-iliac joints are the anatomic basis for the movements of the pelvic joints in pregnancy and labor. During pregnancy a relaxation of the strong ligaments in the sacro-iliac joints and the symphysis pubis occurs and makes possible an increased mobility. The importance of this increased mobility lies in the possibility of a change in size of the pelvic ring. This relaxation also prevents, to a certain degree, the forcible rupture of the ligaments, which under physiologic conditions are only slightly extensible.

The mobility of the pelvic joints and especially of the symphysis pubis in pregnancy was well known to Hippocrates, who spoke of the separation of the ossa pubis during labor. Morgagni, Spiegel and Harvey held the same opinion. Barkow<sup>1</sup> (1841), Luschka<sup>2</sup> (1864), Balandin (1871) and others likewise recognized this fact. Martius<sup>3</sup> (1930) and Müller<sup>4</sup> were able to give proof of the widening of the

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From the Pathological-Anatomical Institute of the University of Innsbruck.

1. Barkow, quoted by Luschka, H.: *Die Kreuzdarmbeinfuge und die Schambeinfuge des Menschen*, Virchows Arch. f. path. Anat. **7**:299, 1854; quoted by Klein, G.: *Zur Mechanik des Ileosacralgelenkes*, Ztschr. f. Geburtsh. u. Gynäk. **21**:74, 1891; footnote 2.

2. Luschka, H.: *Die Anatomie des Menschen: Die Anatomie des menschlichen Beckens*, Tübingen, H. Laupp, 1864, vol. 2, p. 88.

3. Martius, H.: *Umbauformen und andere Anomalien der unteren Wirbelsäule und ihre pathogenetische Bedeutung*, Arch. f. Gynäk. **139**:581, 1930.

4. Müller, W.: *Röntgenologische Untersuchungen über die Symphyse Schwangerer*, Zentralbl. f. Gynäk. **55**:999, 1931.

symphysis pubis by roentgen studies made immediately after labor, and by additional roentgenograms made six weeks post partum they demonstrated the reduction in the width of this point.

Different opinions exist regarding the manner of relaxation of the joints. According to R. Fick<sup>5</sup> the relaxation of the joints of the pelvic ring is due to a shifting of the center of gravity of a pregnant woman, and through this shifting, the posture is changed. Furthermore, during pregnancy the mobility of the symphysis is augmented in walking. This theory of Fick is corroborated by a comparative study of the symphysis pubis of men. Likewise, a greater mobility of the pelvis in its anterior part necessitates an increased gaping of the sacro-

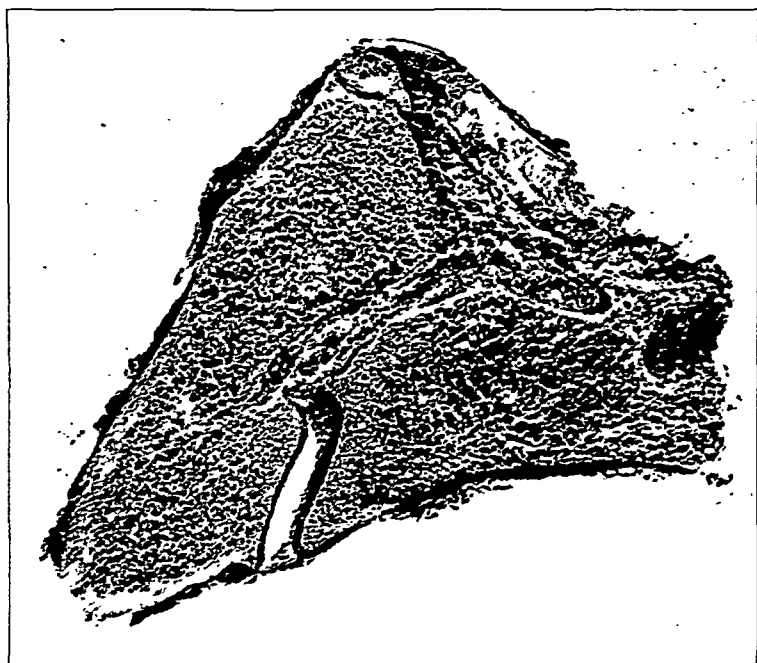


Fig. 1.—Gross specimen of a gaping articulation sacro-iliaca during the second pregnancy of a 20 year old woman.

iliac joints. Thus the anterior ligaments of the sacro-iliac joints and the ligaments of the symphysis pubis are stretched, while the posterior sacro-iliac ligaments are relaxed. This increased mobility is utilized during labor and, if insufficient, may be augmented by the operative procedure of pubiotomy. Following such an operation the anterior sacro-iliac ligaments prevent widening beyond a certain point.

The mobility of the pelvis in pregnancy has been proved by roentgen studies made during this period. Von Schubert<sup>6</sup> demonstrated, by

5. Fick, R.: Bemerkungen über die Höhlenbildung im Schamfugenknorpel, *Anat. Anz.* **19**:307, 1901.

6. von Schubert, E.: Röntgenuntersuchungen des knöchernen Beckens im Profilbild: Exakte Messung der Beckenneigung beim Lebenden, *Zentralbl. f. Gynäk.* **53**:1064, 1929.

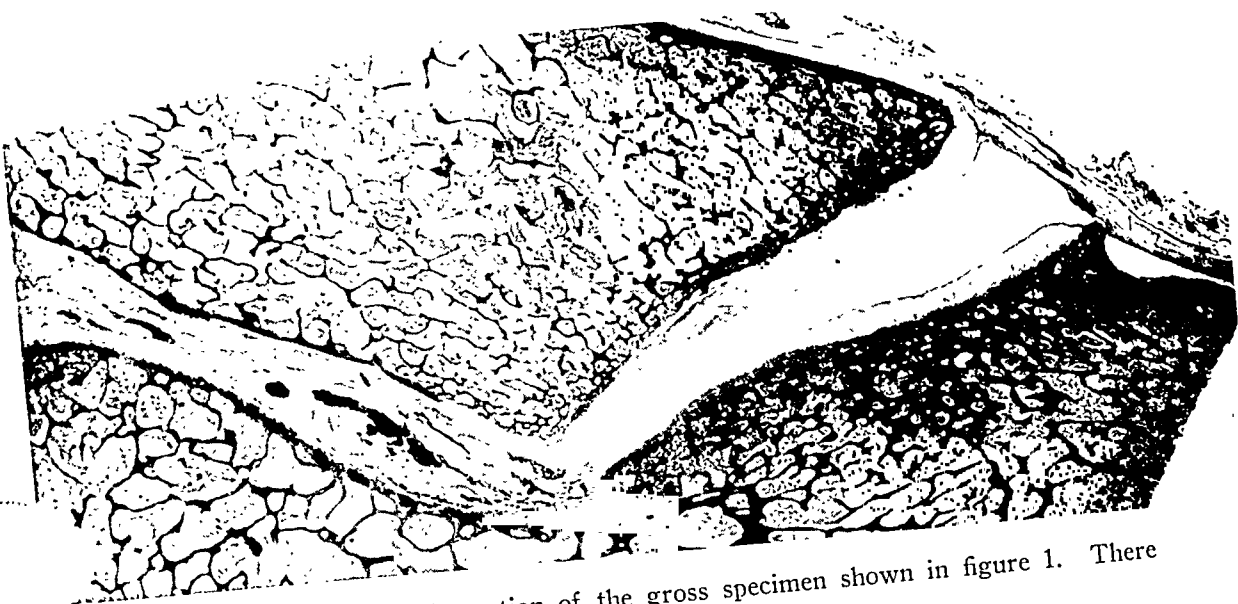


Fig. 2.—Microscopic section of the gross specimen shown in figure 1. There is considerable gaping of the joint.

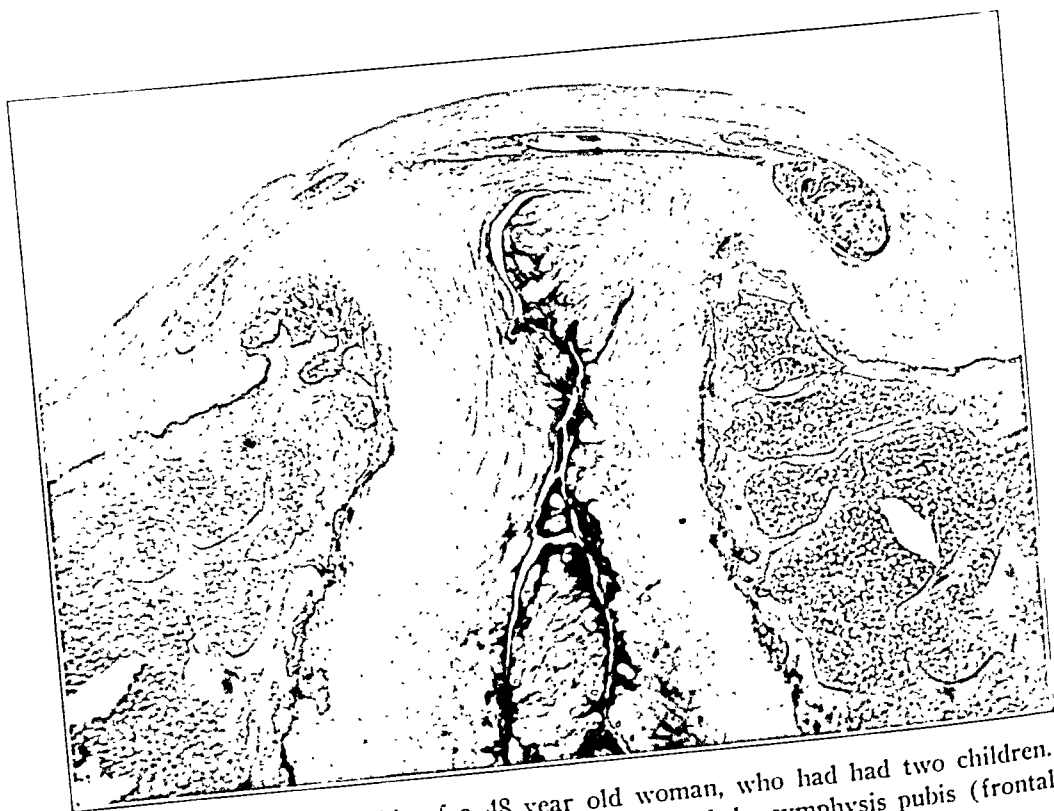


Fig. 3.—Symphysis pubis of a 48 year old woman, who had had two children. Cyst formation is visible near the terminal portions of the symphysis pubis (frontal section).

his researches on women at full term in the erect and prone positions, that the angle between the conjugata anatomica and the sacrum was from 5 to 8 degrees greater when the patient was standing. With the patient lying down, the conjugata vera was lengthened from 5 to 7 mm. Thus, clinical as well as anatomic observations show a possibility of widening of the pelvis during pregnancy and labor. This possibility of the considerable widening of the pelvic joints was clearly demonstrated by our own researches, consisting of roentgenograms, horizontal



Fig. 4.—Part of the ossification zone of the symphysis pubis of a 15 year old girl with depression of the ossification line due to degeneration of the ground substance of the cartilage.

sections and histologic study of cross-sections and of the joints. At the end of pregnancy and shortly after labor the joints were gaping (figs. 1 and 2).

The correctness of the findings of Fick concerning the mobility of the pelvic joints was substantiated by histologic studies. Enlargement of the cavity of the symphysis pubis as a result of increased activity has been found in men following heavy work. Thus it follows that this increased mobility is chiefly caused by mechanical strains and changes of posture.

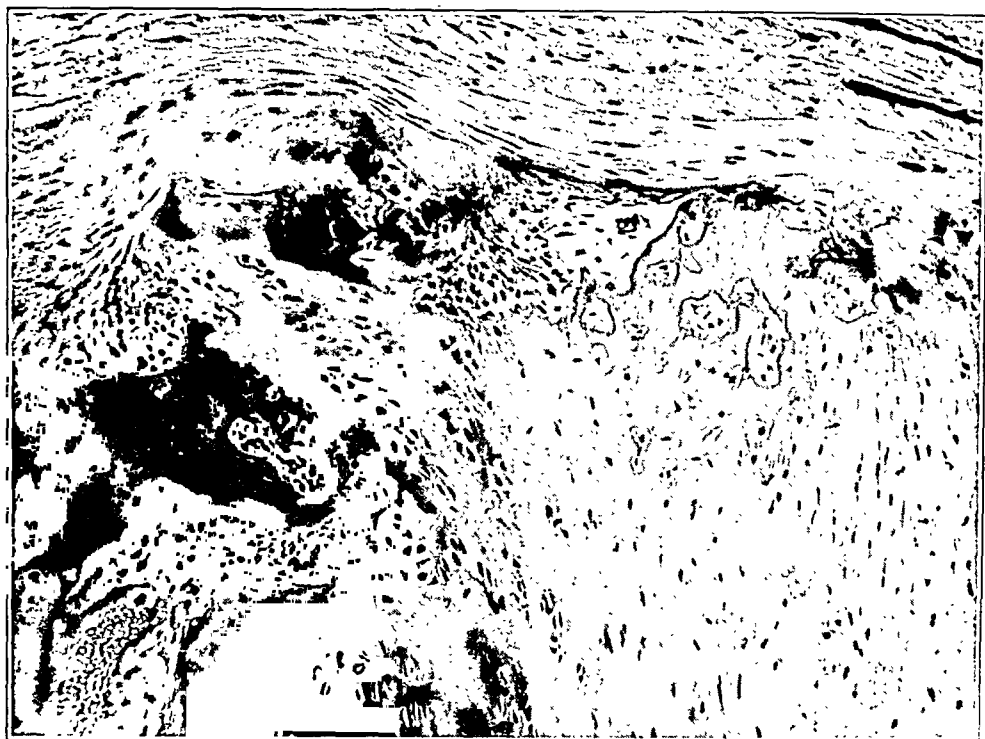


Fig. 5.—Microscopic fracture in the terminal parts of the symphysis pubis of an 11 year old girl.



Fig. 6.—Part of an articulation sacro-iliaca of a 36 year old woman who had had seven children. Fissure formation in the joint cartilage is seen.

A further proof of increased mobility of the sacro-iliac joints and symphysis pubis is given by the frequent finding of cysts. These cysts are situated near the terminal portions of the joints (fig. 3); the lining is often partly synovial. About the symphysis pubis they are often situated beneath the soft tissues and the periosteum. Many of them are directly connected with the joint space. Within the cysts are small rounded fragments of cartilage and bits of tissue of varying size which have come from within the joints, the result of the rubbing together of the joint surfaces. The fragments often accumulate in the outer angles of the cysts and frequently lie in striae within the cysts,

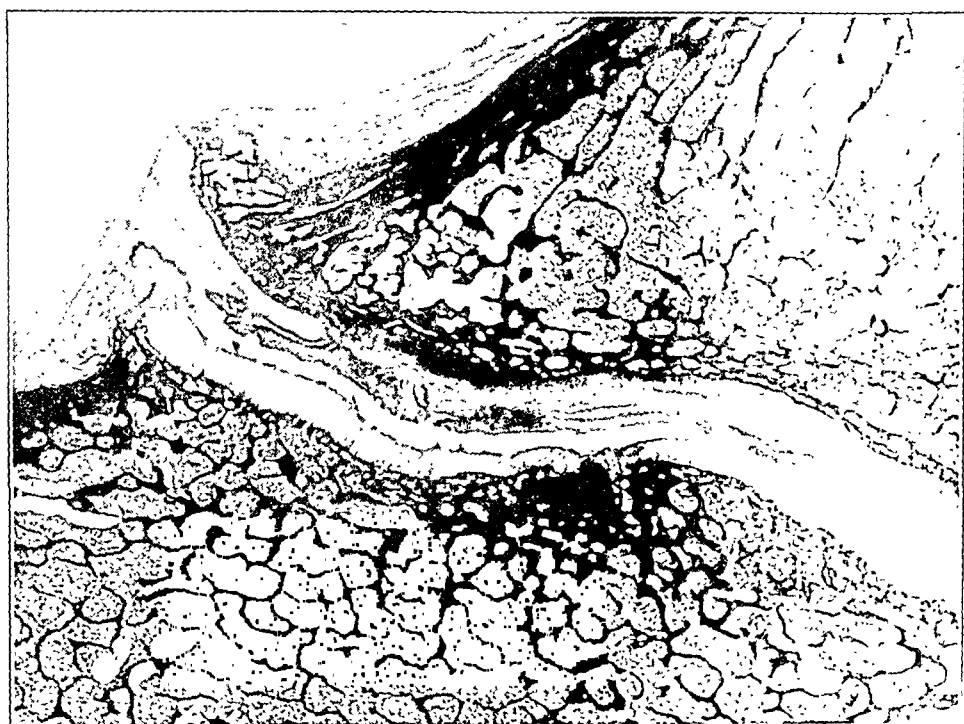


Fig. 7.—Articulatio sacro-iliaca of a 27 year old woman who had had two children. Note the formation of marginal exostoses at the terminal parts of this joint. Hemorrhage has occurred in the joint cavity.

indicating that they have been given off by the joint at different intervals. The formation of these cysts and the character of their lining and contents indicate a certain necessity for mobility of these joints. Of further importance is the fact that none of the sacro-iliac joints and scarcely any symphysis pubis investigated were free from pathologic changes. A distinction must be made between the changes due to trauma and those due to osteoarthritis deformans, as well as to secondary diseases of the joints. In children and young persons up to the time of the completion of ossification, small areas of liquefaction and mucoid degeneration of the ground substance of the cartilage

occur. Ossification does not progress in these foci, and the result is an indentation or depression in the zone of ossification (fig. 4). These effects of mechanical trauma are especially well seen in the terminal parts of the joints; they are characterized by numerous minute areas of damage, microscopic fractures, fissure and cyst formation and hemorrhages (fig. 5). The result of such injuries is the separation and rounding off of fragments and callus formation. Pregnancy affords

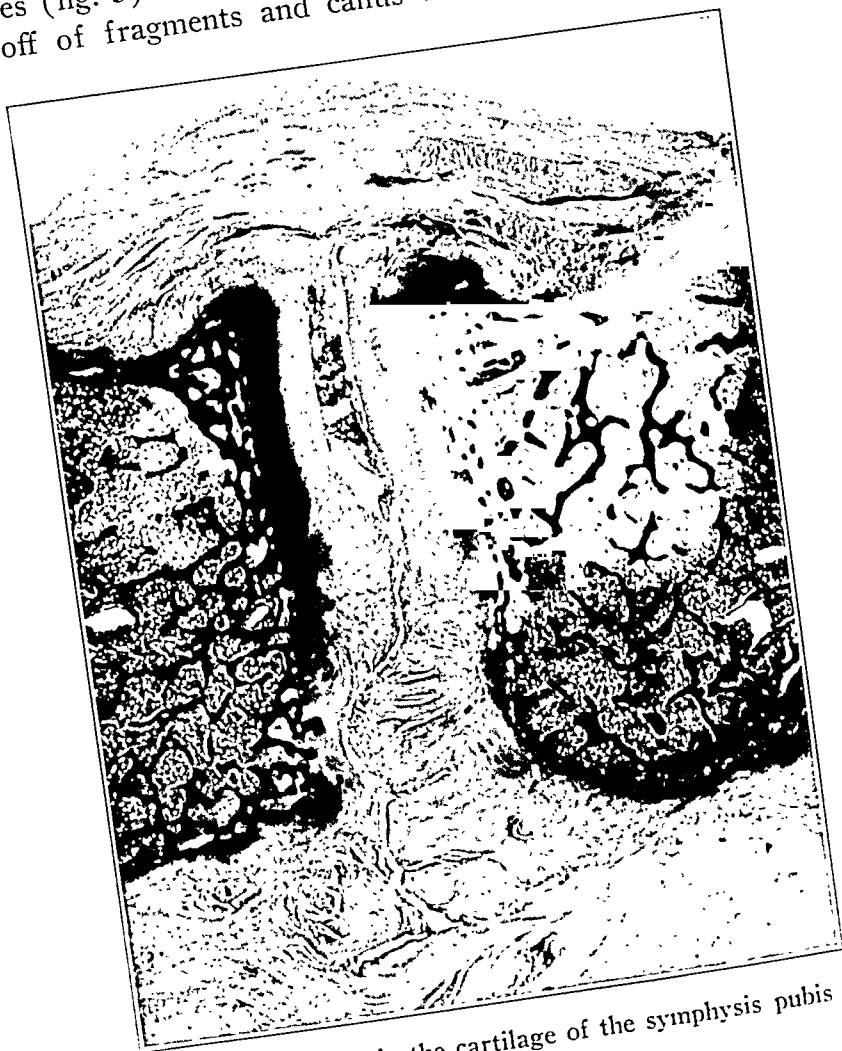


Fig. 8.—Fissure formations in the cartilage of the symphysis pubis of a 36 year old woman who had had seven children.

the opportunity for the occurrence of slight traumas with sequelae similar to those first described in studies of arthritis deformans of the hip joint (Lang<sup>7</sup>). Because of the greater hyperemia and increased vulnerability of the pelvic tissues during pregnancy, functional activity is more irritating and increasingly so toward the end of pregnancy. If

7. Lang, F. J.: Mikroskopische Befunde bei juveniler Arthritis deformans. Virchows Arch. f. path. Anat. **239**:76, 1922; Zur Kenntnis der Veränderungen der Hüpfanne bei Arthritis deformans, ibid. **252**:578, 1924.

changes remain from previous pregnancies or if changes of a static or mechanical nature, as for example a lordosis, are present, such changes can be accentuated during subsequent pregnancies and labors.

Functional or traumatic changes, especially in the cartilage of the pelvic joints, are of great importance for the origin of reactive and proliferative processes of arthritis deformans in these joints. Apart from the lacerations and fissure formations resulting from successive pregnancies and labors, the sequelae of traumatic changes remaining from childhood are especially noteworthy for the production of arthritis deformans. All the characteristics of arthritis deformans can be

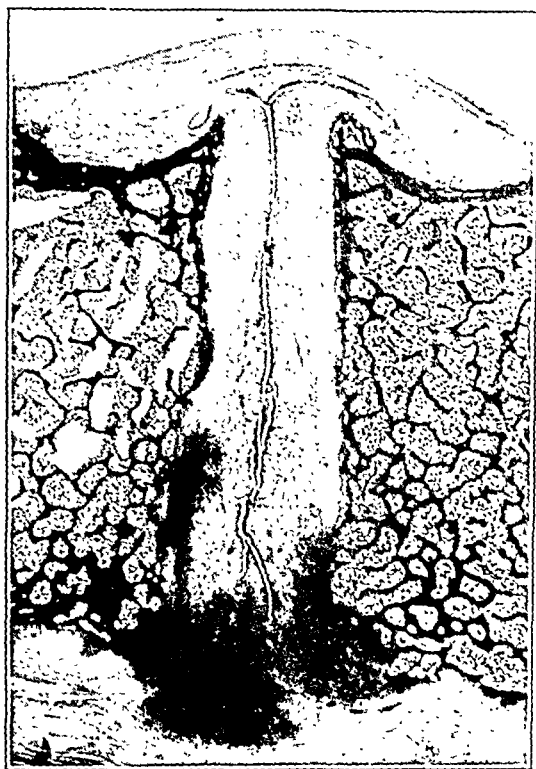


Fig. 9.—Symphysis pubis of a 52 year old woman who had had three children. The formation of a T-shaped cleft is seen (see fig. 10).

observed, namely, changes in the cartilage with loss of its normal elasticity (fig. 6), vascularization and ossification invading the cartilage from the subchondral zone, extreme erosion of the surface with polishing and the formation of marginal exostoses (fig. 7). The so-called growth processes in the pelvis bones during pregnancy can be traced to reactive processes that arise from damage to the cartilage. These injuries to the cartilage are accompanied by vascularization and formation of bone in the deeper parts of the cartilage.

Changes that must be considered as a permanent dilatation of the pelvis are found in the extensive fissure formations and T-shaped



clefts of the symphysis pubis (figs. 8 to 10). These can be seen at the end of pregnancy and in women who have given birth to full term infants. In like manner, the occasionally observed true joint of the symphysis pubis is the result of an adaptation to functional activity.

Marked differences can be shown in the symphyses pubis of women at the end of pregnancy and shortly after delivery, as contrasted with those of women who have had a delivery several years previously. In the symphysis pubis of a woman at the end of pregnancy and shortly after labor, extensive splitting of the cartilage lining the joint is found. Such splitting is not present in the cartilage of the symphysis pubis of

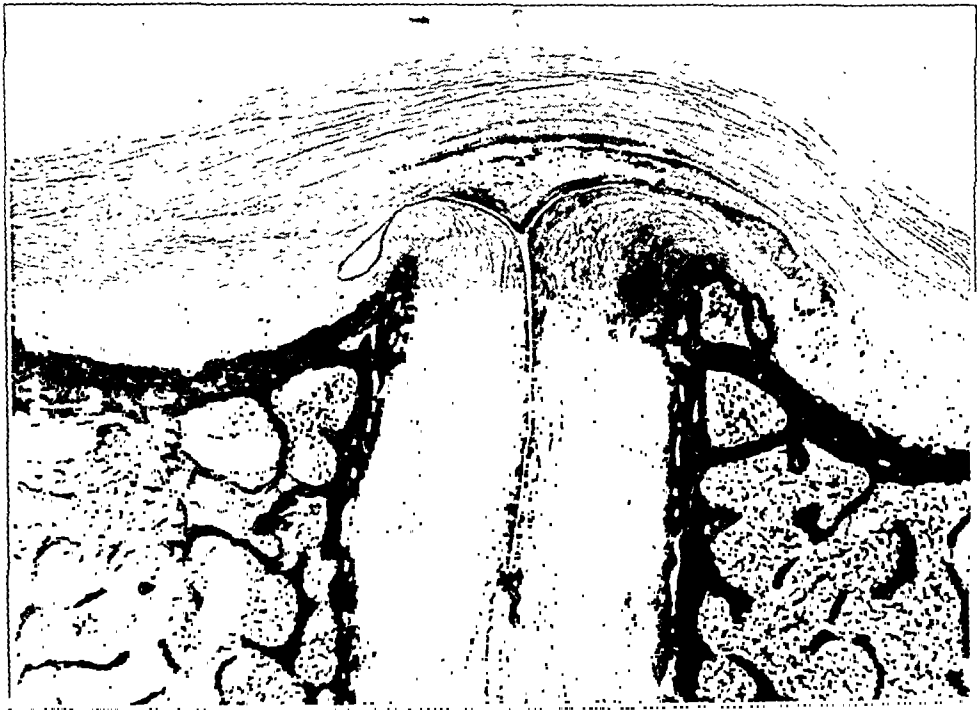


Fig. 10.—Part of area shown in figure 9, with the T-shaped cleft in the inner part of the symphysis.

a woman who has had a delivery years before. Instead the surfaces of the cartilage are smooth and approximated. It appears that the split cartilage becomes entirely separated and is forced out into the cysts; the fragments of cartilage and tissue clearly prove this.

The finding of recent and old hemorrhages in the cavities of the sacro-iliac joints must be mentioned. The hemorrhages are the result of trauma to these joints. Larger hemorrhages are found as the sequel to the disproportion between normal extensibility of the joint and that due to necessity (fig. 5). They follow trauma during labor, and furthermore can arise from the increased stress on the ligaments occurring at the end of pregnancy. The hyperemia of the ligaments and the

synovial tissues during pregnancy explains the extravasations of blood as congestive hemorrhages.

The investigations discussed prove that changes in the sacro-iliac joints must be considered as a cause of the backache that is so frequent in pregnant women and in those who have had many labors. This fact has recently received increased attention from gynecologists and orthopedic surgeons following the demonstration that backache can result from anatomic changes of the vertebrae and their connections with the sacro-iliac joints.

#### CONCLUSIONS

These studies place on an anatomic and histologic basis the clinically recognized gaping of the pelvis in pregnancy and labor. They show the development of this widening and the alterations that the pelvic joints thereby suffer. They present the late sequelae leading directly or indirectly to permanent changes in the joints. Finally, they indicate that pregnancy and labor, with their disturbances of the static mechanical relationships of the pelvis, are not inconsequential factors in the etiology of arthritis deformans.

# SYPHILIS OF THE STOMACH

## REVIEW OF THE LITERATURE AND REPORT OF A CASE

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Although the clinical diagnosis of syphilis of the stomach is made frequently and such cases are reported in large numbers, histologically proved instances of the disease are rare. A case seen recently at the University of Virginia Hospital seems to present sufficient histologic evidence of syphilis of the stomach to warrant a report and a brief review of the stricter criteria demanded for the diagnosis.

An idea of the apparent rarity of proved instances of the disease may be gained from Hartwell.<sup>1</sup> In 1925, he reviewed more than 200 cases that had been recorded previously in the literature as syphilis of the stomach, and he concluded that in all but 27 of these the evidence presented was insufficient to prove the diagnosis. Hartwell's review of the subject was comprehensive and scientifically critical. He stated that Andral<sup>2</sup> had reported 2 cases of supposed syphilis of the stomach as early as 1834. To Chiari,<sup>3</sup> however, he attributed the first significant contribution to the subject. Chiari had emphasized the rarity of histologically proved cases and had found only 7 previously reported cases that conformed to the strict criteria that he promulgated.

Following the introduction of the Wassermann reaction (1906) and gastro-intestinal roentgenology (1909-1912), however, numbers of cases were reported, the diagnosis based, all too frequently, on purely presumptive or insufficient and unsound clinical evidence. Many reports contain no more convincing evidence than the combination of an upper abdominal complaint, roentgenologic evidence of gastric disease and a positive Wassermann reaction. Graham<sup>4</sup> reported the first histologically proved case in which the tissues had been removed surgically.

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1. Hartwell, J. A.: Syphilis of the Stomach: A Critical Review of Reported Cases from the Pathological and Clinical Viewpoints, *Ann. Surg.* **81**:767, 1925.

2. Andral, Gabriel: *Cliniques*, Paris **2**:201, 1834; quoted by Hartwell (footnote 1).

3. Chiari, H.: Ueber Magensyphilis, *Internat. Beitr. z. wissensch. Med. Festschr. R. Virchow* **2**:295, 1891.

4. Graham, E. A.: Surgical Treatment of Syphilis of the Stomach, *Ann. Surg.* **76**:449, 1922.

Necropsy statistics reveal a low incidence of the disease, even among syphilitic patients. Symmers,<sup>5</sup> in a series of 4,880 necropsies, found 314 syphilitic patients, but among these only 1 case of gastric syphilis. Singer and Meyer<sup>6</sup> stated that in 5,000 necropsies, with almost 10 per cent syphilitic patients, no case of gastric syphilis had been found. During the same six year period, however, 4 cases of histologically proved gastric syphilis had been discovered at operation. They attributed the greater surgical incidence of the disease to the increase in the frequency of resection of the stomach in recent years. Furthermore, these data led them to believe that retrogression or healing of gastric syphilis may occur. Study of their resected specimens substantiated this hypothesis. In the same stomach they differentiated various phases of syphilis, from changes characteristic of the height of the tertiary stage to those of dense fibrous overgrowth with widely scattered accumulations of round cells the syphilitic origin of which it was difficult to prove.

The type of case that has been responsible for the greatest confusion in the literature is that in which the history, the roentgenologic and laboratory findings, the resistance to all forms of treatment except specific and the prompt response to antisymphilitic treatment have made the diagnosis of syphilis of the stomach seem probable and reasonable. No doubt syphilis of the stomach has actually existed in some of these instances. In many of them, however, a subsequent necropsy has failed to disclose histologic proof.

For this reason all pathologists and many clinicians now insist on histologic proof of the diagnosis. In this connection it is interesting to note that *spirochaeta pallida* has been found in only 1 of the reported cases. McNee<sup>7</sup> found the organisms in the wall of the stomach, but only after prolonged search through many sections taken from various portions of the stomach and stained by the Levaditi technic.

#### CLINICAL FEATURES

Hartwell, after a careful study of the literature, felt that "there are no characteristic subjective symptoms or objective findings upon which a diagnosis of syphilis of the stomach may soundly rest." He stated 5 clinical features that, when found in combination, had been considered more or less diagnostic: (1) positive Wassermann reaction; (2) a gastric anacidity or markedly reduced hydrochloric acid content;

5. Symmers, Douglas: *Anatomic Lesions in Late Acquired Syphilis: A Study of 314 Cases Based on the Analysis of 4,880 Necropsies at Bellevue Hospital*, J. A. M. A. **66**:1457 (May 6) 1916.

6. Singer, H. A., and Meyer, K. A.: *Syphilis of the Stomach, with Special Reference to Its Incidence*, Surg., Gynec. & Obst. **48**:23, 1929.

7. McNee, J. W.: *Syphilis of the Stomach*, Quart. J. Med. **15**:215, 1921-1922.

(3) marked deformity of the stomach roentgenologically, particularly of the "dumb-bell" type, or with an abrupt margin between the healthy and diseased portions of the stomach; (4) less marked cachexia, emaciation and anemia than would be found with such radiographic changes due to lesions other than those of syphilis; (5) improvement under antisyphilitic treatment. Each of these, however, was shown to be inconstant and undependable.

#### RADIOLOGICAL CHANGES

Carman<sup>8</sup> mentioned 8 suggestive radiologic changes:

(1). Filling defect of the gastric outline, usually without corresponding palpable mass. (2). Shrinkage of gastric capacity. (3). Stiffening and lessened pliability of the gastric wall. (4). Absence of peristalsis from the involved area. (5). Pylorus gaping rather than obstructed. (6). Six-hour retention less common than in other gastric lesions (23 per cent). (7). So-called hour glass stomach; upper loculus expanded and bulbous, lower one tubular, due to extensive, irregular, concentric contraction. (8). Patient usually under cancer age and not ill in proportion to the extent of disease shown by the X-ray.

He felt, however, that these suggestive radiologic signs were much more uncertain even than the clinical signs.

#### HISTOLOGIC CRITERIA

Accurate pathologic descriptions have been given by Chiari,<sup>3</sup> Flexner,<sup>9</sup> Stolper,<sup>10</sup> Pappenheimer and Woodruff,<sup>11</sup> McNee<sup>7</sup> and Brams and Meyer.<sup>12</sup> The disease apparently is initiated by the formation of a gumma in the submucosa and extends from there into the other coats. Through the breaking down of the gumma, particularly because of the action of the gastric juice, ulcers and ultimately scars may form; then only by the finding of other gummas or the remains of gummatous tissue can the syphilitic nature be established.

Grossly, the involved portion of the stomach is usually markedly thickened, most of the proliferation being present in the submucosal

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8. Carman, R. D.: Syphilis of the Stomach in Its Roentgenologic Aspects, *Am. J. Syph.* **1**:111, 1917; *Roentgenologic Aspects of Hour-Glass Stomach*, *Surg., Gynec. & Obst.* **27**:426, 1918.

9. Flexner, S.: Gastric Syphilis, with a Report of a Case of Perforating Syphilitic Ulcer of the Stomach, *Am. J. M. Sc.* **116**:424, 1898.

10. Stolper, P.: *Beiträge zur Syphilis visceralis, Magen-, Lungen- und Herz-syphilis*, Cassel, T. G. Fisher & Company, 1896, pp. 43; quoted by Hartwell (footnote 1).

11. Pappenheimer, A. M., and Woodruff, I. O.: A Case of Syphilis of the Stomach, *M. & S. Rep. Bellevue Hosp.* **2**:219, 1905-1906; quoted by Hartwell (footnote 1).

12. Brams, W. A., and Meyer, K. A.: Gastric Syphilis: A Report of Two Cases Proved Anatomically, *Surg., Gynec. & Obst.* **37**:127, 1923.

layer. Ulceration is usually found, but it may differ in no distinctive way from that of a simple gastric ulcer. Suggestive features are a tendency to be quite large, an irregular serpiginous border, a firm smooth base and a demonstrable thickening of the wall of the stomach at a considerable distance from the ulcer itself. Unbroken gummas may be found occasionally.

Microscopically, gummas are of course most surely diagnostic. Other changes consist of endarteritis, endophlebitis, obliterating endarteritis and infiltration, especially the perivascular "signet-ring" type, with lymphocytes, plasma cells and eosinophilic leukocytes. Occasional giant cells may be found. Turnbull<sup>13</sup> sounded a note of warning against mistaking the similar pathologic changes following chronic inflammations due to pyogenic organisms with the changes due to syphilis.

#### REPORT OF CASE

*History.*—H. E. F., a white man, aged 48, unmarried, was admitted to the University of Virginia Hospital on Nov. 25, 1929, complaining of "stomach trouble" of eight months' duration. In March, 1928, he had begun to suffer with a gnawing sort of pain in the upper part of the abdomen, especially on the left side. The pain had been most severe shortly after the ingestion of a meal, particularly the midday meal. Drinking milk or taking soda had given partial, temporary relief. Vomiting had occurred frequently, and he had lost 40 pounds (18 Kg.). There had been no hematemesis, melena, jaundice or clay-colored stools.

He had first consulted a physician in May, 1929, and had been told that he had "gastritis." He had consulted two other physicians without relief, and finally in September, 1929, a fourth physician had advised a roentgenologic examination of the stomach. This examination had revealed a "growth in the stomach" that had been taken to be malignant. The patient was referred to me for surgical treatment.

The patient's past history was irrelevant except for two attacks of gonorrhea several years previously and a chancre on the penis three years prior to the time of admission. There had been no cutaneous rash and no antisyphilitic treatment except for an ointment applied to the primary lesion. The chancre had healed in about ten days.

*Examination.*—Examination revealed a rather emaciated white man with dry skin and some loss of strength. His temperature was normal. The systolic blood pressure was 135, the diastolic 80. The mucous membranes were not pale; the sclerae were not bile tinged. The pupils were regular, and equal in size, but reacted somewhat sluggishly to light and in accommodation. The teeth were carious, and there was some pyorrhea alveolaris. There was no glandular enlargement. The heart and lungs were apparently normal. The abdomen was scaphoid. The edge of the liver was palpable. There was a movable, slightly tender mass about 5 cm. in diameter situated in the epigastrium just to the left of the midline. Both inguinal rings were very large, and there was some herniation. The patellar and other reflexes were normal.

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13. Turnbull, in discussion on Monod, G.: Syphilis of the Stomach, Proc. Roy. Soc. Med. **15**:1, 1921-1922; quoted by Hartwell (footnote 1).

Urinalysis revealed no abnormality. The hemoglobin was 80 per cent (Dare); the red corpuscles numbered 4,360,000, the leukocytes 4,400, and the smear did not show any abnormality. The Wassermann reaction of the blood was strongly positive on several occasions. The stool contained no blood. Gastric analysis demonstrated marked retention without evidence of free hydrochloric acid. Lactic acid, occult blood and Oppler-Boas bacilli were present in the material. The Wassermann reaction of the spinal fluid was strongly positive. A roentgenologic examination of the chest gave negative results; the results of an examination of the stomach, made on Nov. 27, 1929, were reported as follows: "The esophagus

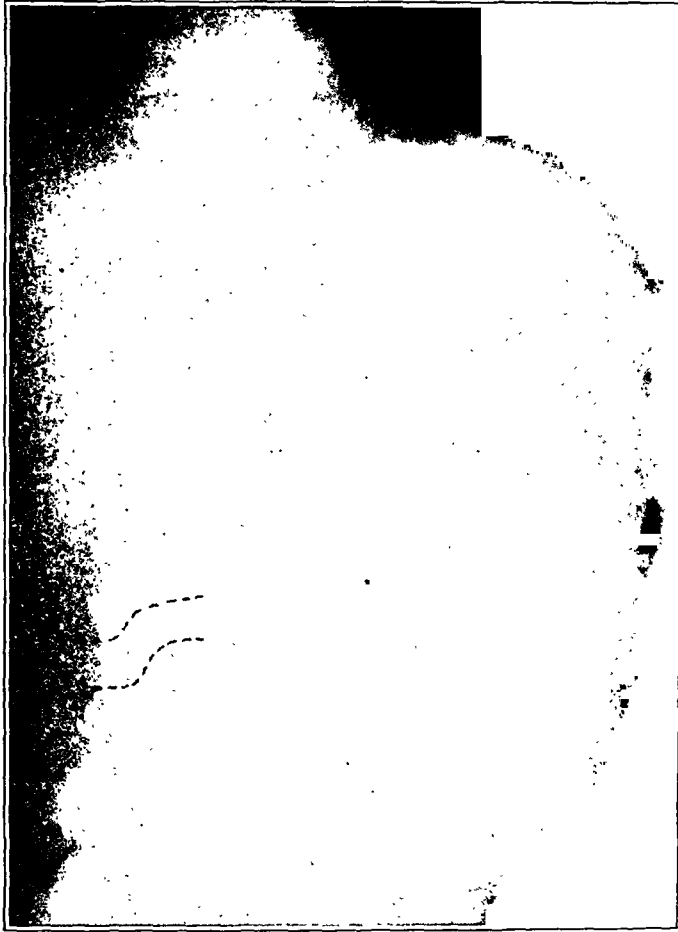


Fig. 1.—Roentgenogram of the stomach, taken on Nov. 27, 1929.

is normal. A large amount of gastric content is present. The stomach is large and, except for some canalization, its lumen is obstructed in the prepyloric region. After six hours a gastric residue estimated at 50 per cent is present. Diagnosis: Probable carcinoma of the stomach with obstruction" (fig. 1).

*Treatment and Course.*—Because of the gastric retention the patient was put at rest in bed; the stomach was emptied, and a liquid and soft, bland diet was prescribed. On this regimen no further vomiting occurred and the fluid balance was maintained satisfactorily. Two small doses of arsphenamine were given intravenously on December 2 and 5, respectively. Reexamination of the blood on December 3 revealed the hemoglobin to be 93 per cent (Sahli) and the red cells,

4,740,000. The stomach was reexamined roentgenologically on December 5, and described as follows: "A canalized lumen is demonstrable between the cardiac and pyloric regions of the stomach. The pyloric region distal to the deformity appears to be fairly normal. The pylorus and duodenum seem to be normal. A six hour gastric residue estimated at 50 per cent is still present. Diagnosis: Carcinoma of the stomach with obstruction" (fig. 2).

Several intravenous injections of physiologic solutions of sodium chloride and dextrose were given during the two days before operation, and on Dec. 7, 1929, under nitrous oxide, oxygen and ether anesthesia, the patient's abdomen was

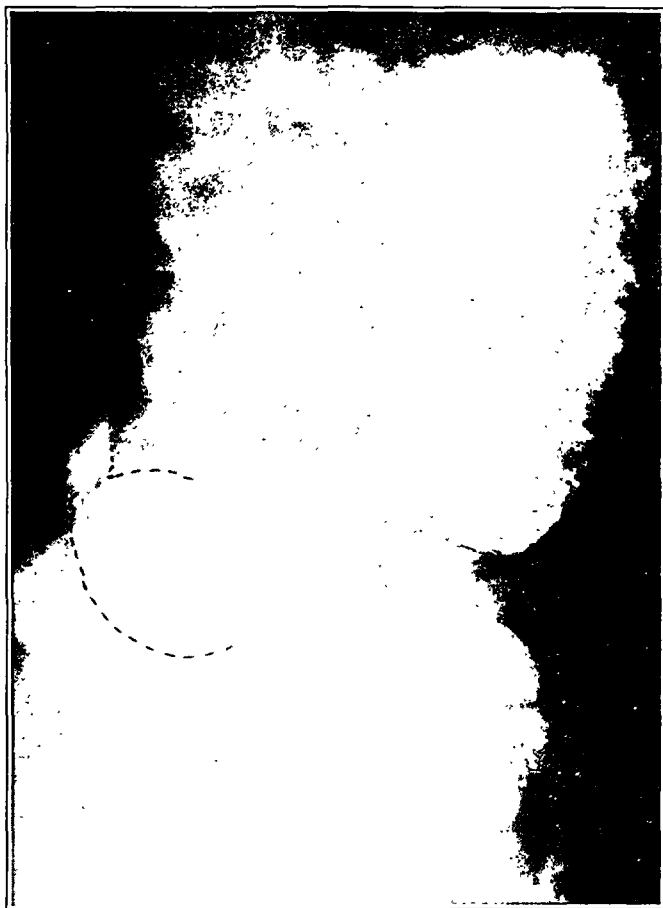


Fig. 2.—Roentgenogram of the stomach, taken on Dec. 5, 1929.

explored. The incision was made through the upper part of the rectus muscle on the right side. Except for the stomach no abnormality of any of the intra-abdominal organs was discovered. There were no nodules in the liver and no enlarged lymph nodes except those immediately adjacent to the stomach. Almost the entire distal two thirds of the stomach was greatly thickened and of a rubbery consistency unlike that of carcinoma. One of many enlarged glands along both the lesser and the greater curvature was excised for immediate examination. A frozen section revealed no gross or microscopic evidence of carcinoma.

A resection of the diseased portion of stomach seemed to be advisable. The duodenum was severed at a point just distal to the pylorus, and the lower two thirds of the stomach was resected. The stump of the duodenum was closed, and



the proximal end of the remaining portion of the stomach was anastomosed with the side of a loop of the jejunum which had been brought up through the transverse mesocolon. The mesocolon was sutured about the stomach just proximal to the anastomosis and the abdomen closed without drainage.

The tissue removed at operation was described in the following pathologic report: "The specimen consists of a resected portion of the stomach about 15 x 11 cm., roughly triangular in shape. The wall of the stomach is greatly thickened throughout. On the mucosal surface is a hemorrhagic, ulcerated and scarred area 8 x 6 cm. with irregular, serpiginous and thickened borders. In its margins there are two small, firm areas and one deeper ulcer about 2 cm. in diameter. The



Fig. 3.—Resected portion of the stomach.

attached gastro-hepatic and gastro-colic omental tissue contains several pea-sized lymph nodes that have a rubbery consistency (fig. 3).

"Microscopically the mucosa at the margins of the ulceration shows round cell, plasma cell and polymorphonuclear infiltration with some hemorrhage. Immediately beneath this there are large collections of round cells and plasma cells. The submucosal layer is markedly thickened, and edematous. In it are much fibrous tissue and numerous cellular areas composed of round cells, plasma cells and centrally located epithelioid cells with occasional giant cells. Collections of cells surround many of the arteries imparting a 'signet-ring' appearance. In some instances the arterial lumen is narrowed and in some completely obliterated by endarteritis (fig. 4). The lymph nodes reveal evidences of acute and chronic inflammation with marked hyperplasia of the follicles. Diagnosis: Syphilis of the stomach with ulceration. Lymphadenitis, acute and chronic."

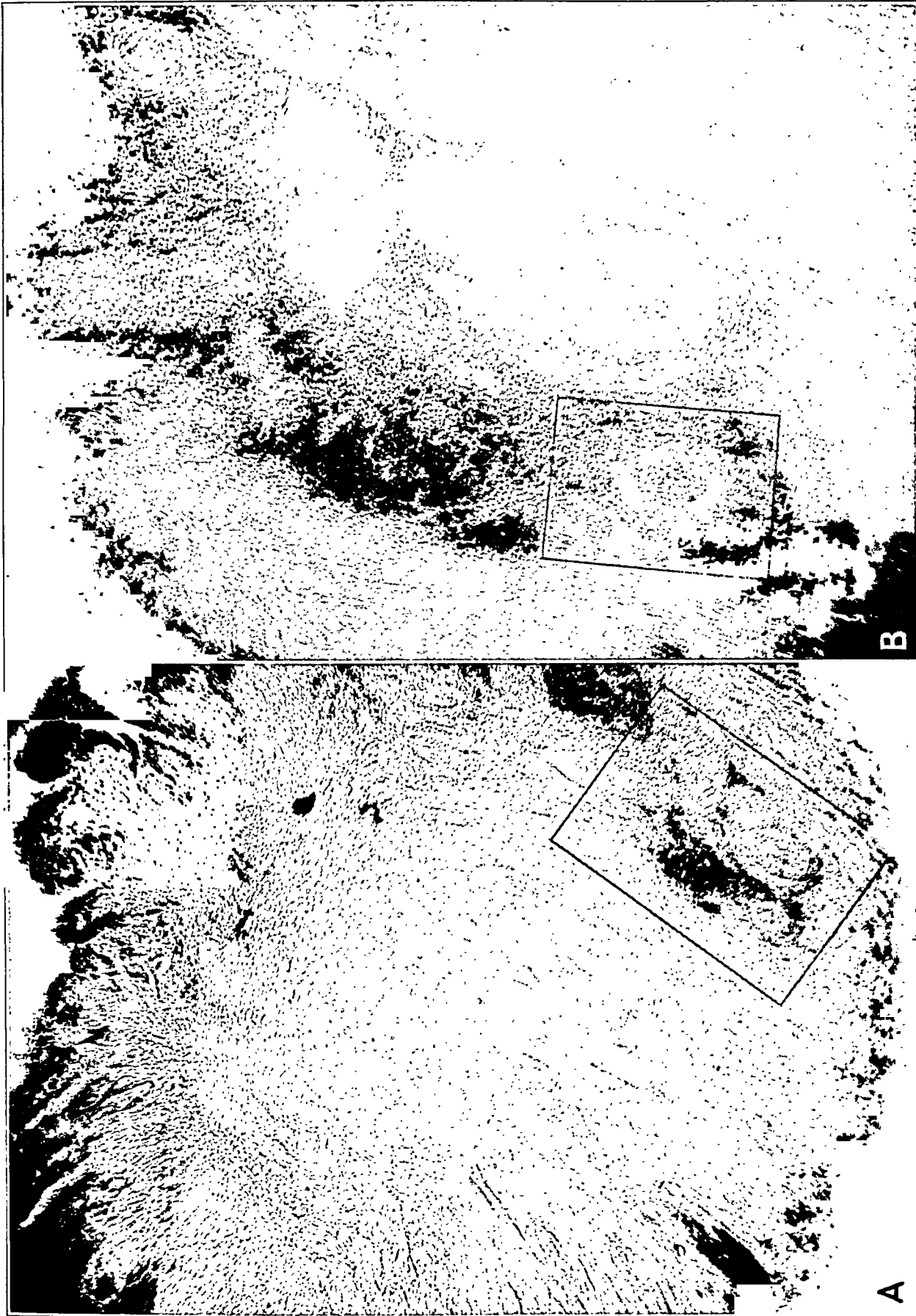


Fig. 4---1, photomicrograph, showing the marked reaction in the gastric wall without ulceration of the mucosa;  $\times 25$ . B, high power view  
.....  $\times 5$



Fig. 5.-A, photomicrograph, showing higher power view of the portion marked in figure 4 B;  $\times 150$ . B, photomicrograph of another area, showing perivascular infiltration and obliterative endarteritis;  $\times 50$ .

Numerous blocks of tissue from various sites in the stomach were studied by the Levaditi technic, but no positively identifiable *spirochaeta pallida* were discovered.

The postoperative convalescence of the patient was uneventful. He was allowed to go home on Dec. 21, 1929, fourteen days after operation. His condition at that time was excellent. He returned for antisyphilitic treatment periodically for four months, during which time he gained 30 pounds (13.6 Kg.).

A last report from the patient, on March 3, 1931, two years and three months after operation, stated that his general health was excellent, that he had no gastric or other abdominal symptoms and that he was able to carry on his former work without difficulty. He was known to be alive and well on Jan. 1, 1932.

#### COMMENT

This case presented many of the clinical and roentgenologic features that have been attributed to gastric syphilis. The histologic characteristics of the portion of stomach removed at operation seem to furnish conclusive proof that the disease was true syphilis of the stomach.

The failure in the search for spirochetes in the tissue was disappointing. In this connection it is impossible to say with certainty what may have been the effect of the preoperative injections of arsphenamine, though it seems likely that they may have caused the disintegration of the spirochetes that might have been present. It might have been worth while to inject some of the tissue into the testis of a rabbit, but this procedure was not thought of until too late. In any similar cases that may be encountered this test will be applied.

#### SUMMARY

A brief review of some of the critical literature on syphilis of the stomach has been given. Attention has been called particularly to the histologic criteria employed in making the diagnosis and the necessity of these histologic proofs. A case of syphilis of the stomach encountered at the operation has been described with the histologic proofs of the diagnosis.

# ADAMANTINOMA

A CASE OF FIFTY-ONE YEARS' DURATION

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AND

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A recent acquisition of the College of Physicians and Surgeons is a large adamantinoma of the lower jaw with a history of fifty-one years' duration. This type of tumor is noted for its slow, persistent growth, but as this history is the longest that we can find on record, the case is presented as one of unusual interest.

Adamantinomas are relatively rare tumors, usually occurring in young people. Grossly they are either solid masses of pale slimy tissue or nodular, part solid and part cystic. They are found within the bone of either the upper or lower jaw, much more frequently in the latter, often in the region of an unerupted tooth, and as they grow cause an expansion of the outer shell of bone. Microscopically, they show a stroma of either adult fibrous tissue or embryonal tissue, similar to that seen in the dental papillae, in which are embedded masses of epithelial cells that approximate the appearance of those of the embryonal enamel organ.

According to Malassez, it is the "epithelial debris" persisting from this organ that is the basis for the tumor. Some of the cells are arranged in sheets, similar to the neck of the primitive organ as it grows down from the alveolar epithelium. Some are in rounded masses similar to the organ itself, the outer cells being arranged radially like the ameloblasts, the inner cells giving a starlike appearance like those of the "stellate reticulum." It is probably the degeneration of these star cells that gives rise to the numerous separate cysts that are frequently found. Occasionally these tumors form teeth. They are slow-growing, difficult to cure, except by radical measures, and apparently may be quiescent for years, as in Porzelt's case, in which the tumor recurred after forty-five years. They rarely metastasize, but exceptional cases with lymph node involvement have been described by Ewing, Simmons and New, and Ewing and Simmons have reported lung metastases.

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From the Laboratories of Surgery, College of Physicians and Surgeons, Columbia University, and the Laboratory of Surgical Pathology, the Presbyterian Hospital.

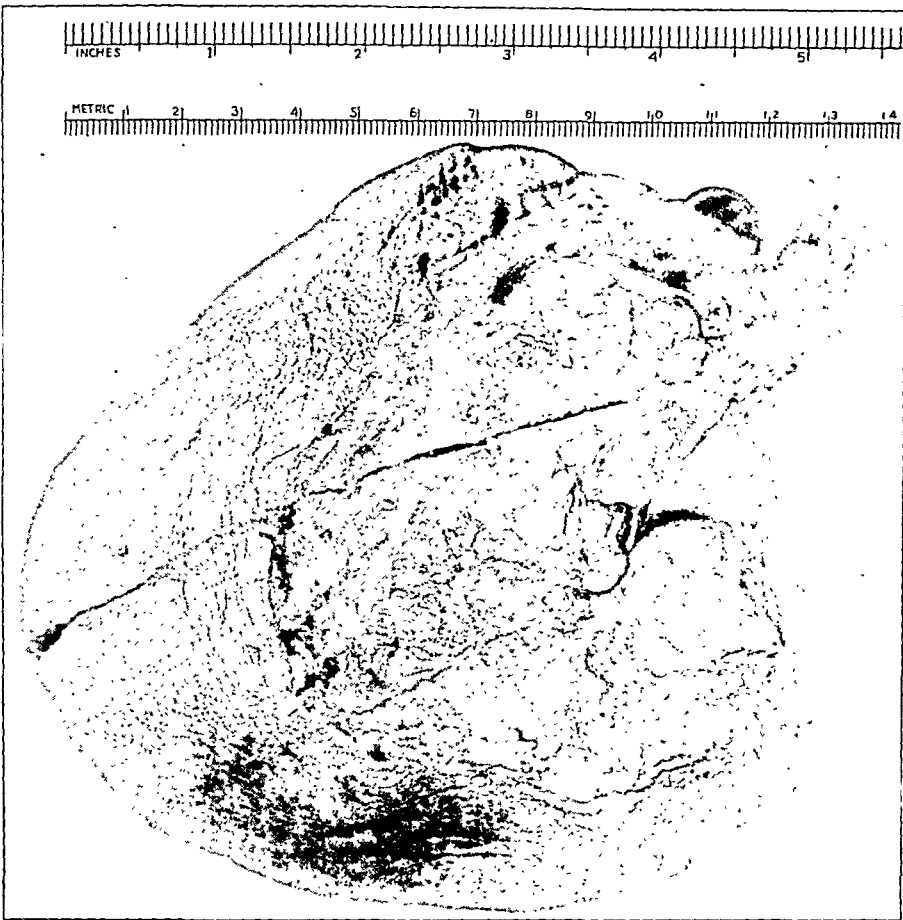


Fig. 1.—Gross photograph of the inferior aspect of the tumor with the remaining portion of the mandible attached.



Fig. 2.—Gross photograph of the tumor bisected. Note the necrotic area in the center and the cystic spaces scattered throughout.

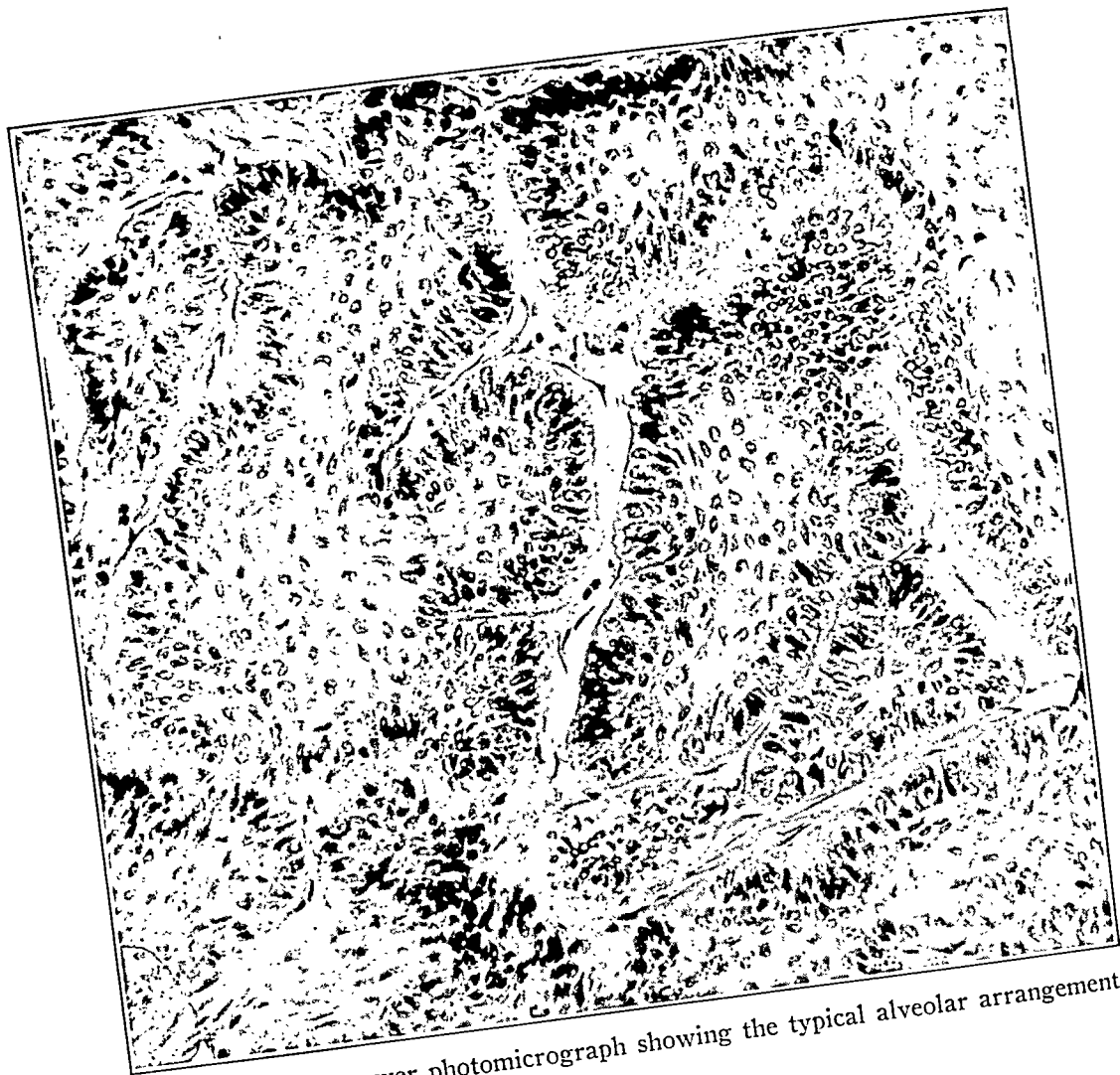


Fig. 3.—Low power photomicrograph showing the typical alveolar arrangement, with connective tissue trabeculae.

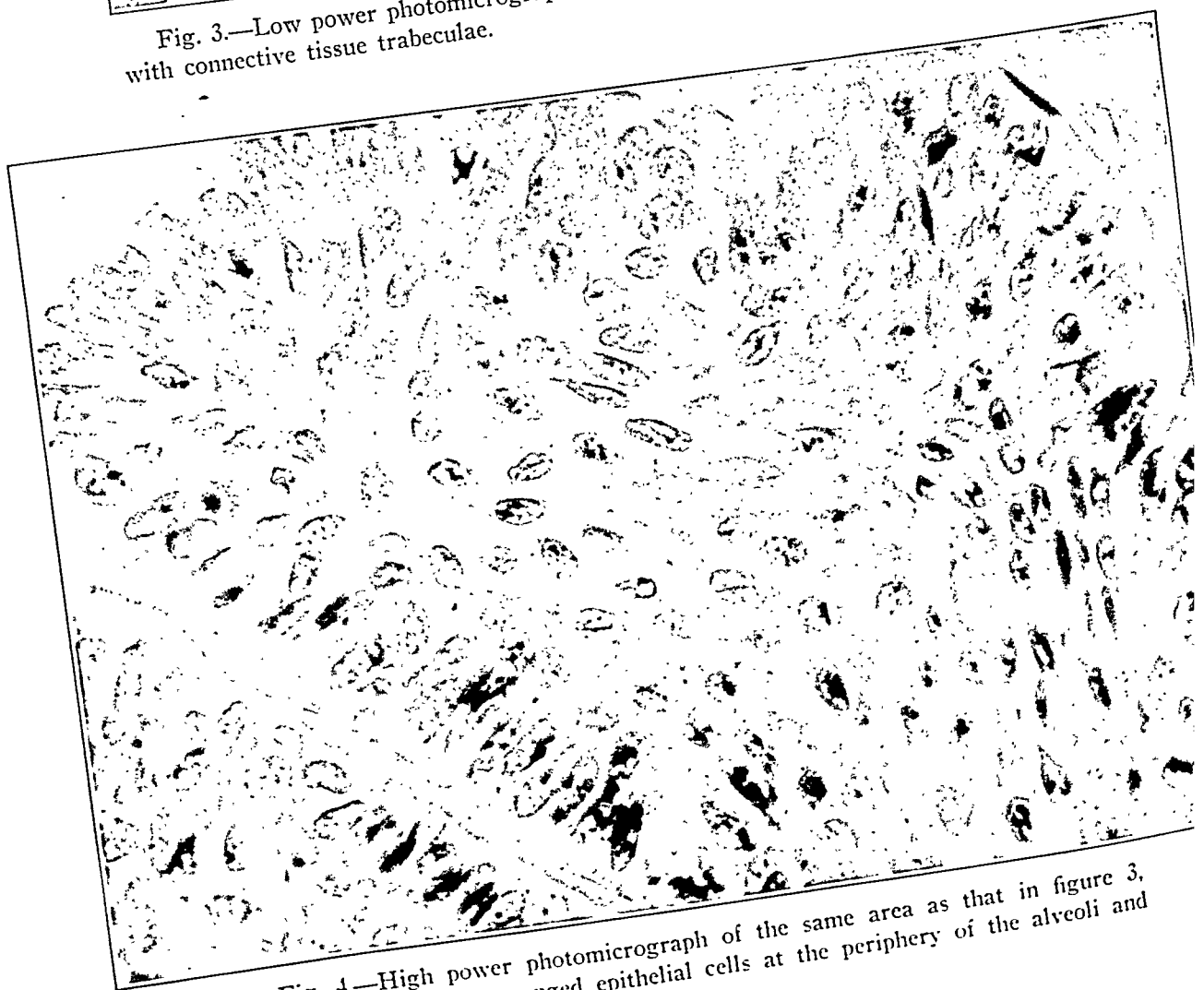


Fig. 4.—High power photomicrograph of the same area as that in figure 3, showing the radially arranged epithelial cells at the periphery of the alveoli and the central cells with intercellular bridges.

## REPORT OF CASE

C. M. L., a woman, aged 32, married, was admitted to the Roosevelt Hospital, New York, on June 22, 1885, complaining of a lump in the right side of the lower jaw.

Seven years previously, in 1878, a carious tooth had been extracted, following which the jaw began to swell gradually without pain or tenderness. Four and a half years after the onset the tumor had reached a large size, was circumscribed and limited to the center of the jaw, and hung down so as to touch the shoulder when the head was turned. It was removed surgically at that time, leaving a

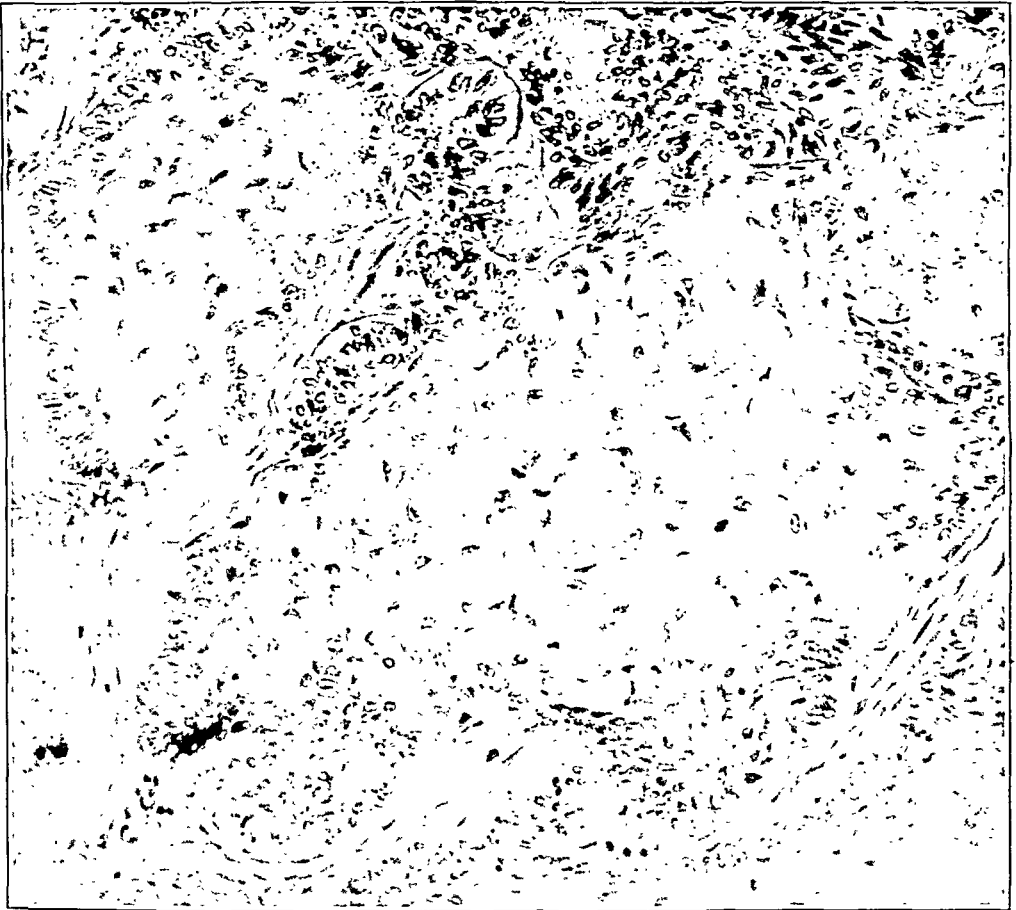


Fig. 5.—Low power photomicrograph showing alveoli in which the central cells have undergone degeneration, probably a precystic phase.

small shell of bone on the lower edge of the jaw and, according to the patient, the source of the tumor on the inner surface. Sequestrums of bone were discharged spontaneously for a year after this operation, and pain began eight months after operation, persisting up to the patient's admission to the hospital. Nine months before admission the pain was somewhat relieved by the surgical drainage of a large abscess situated posterior to the jaw. The tumor steadily increased in size for the nine months previous to admission.

Physical examination on the patient's admission to the Roosevelt Hospital, on June 22, 1885, yielded the following data: "There is a swelling of the lower jaw



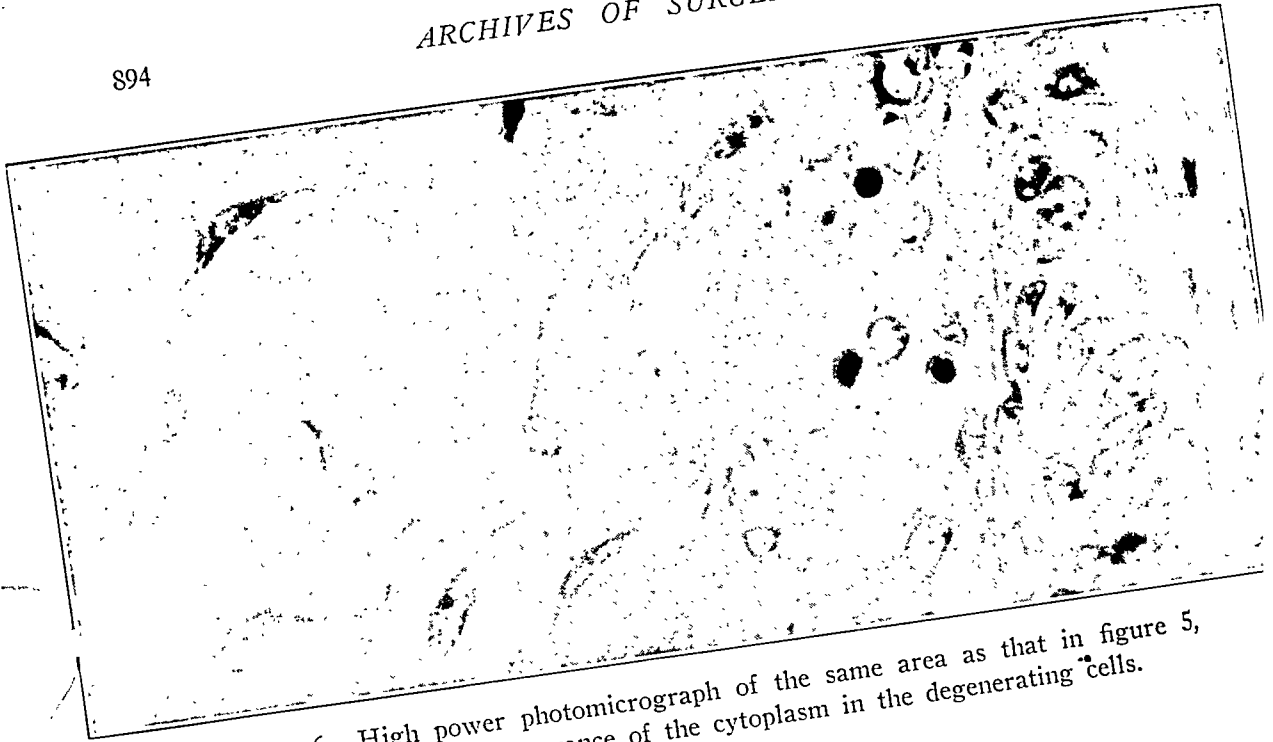


Fig. 6.—High power photomicrograph of the same area as that in figure 5, showing the granular appearance of the cytoplasm in the degenerating cells.

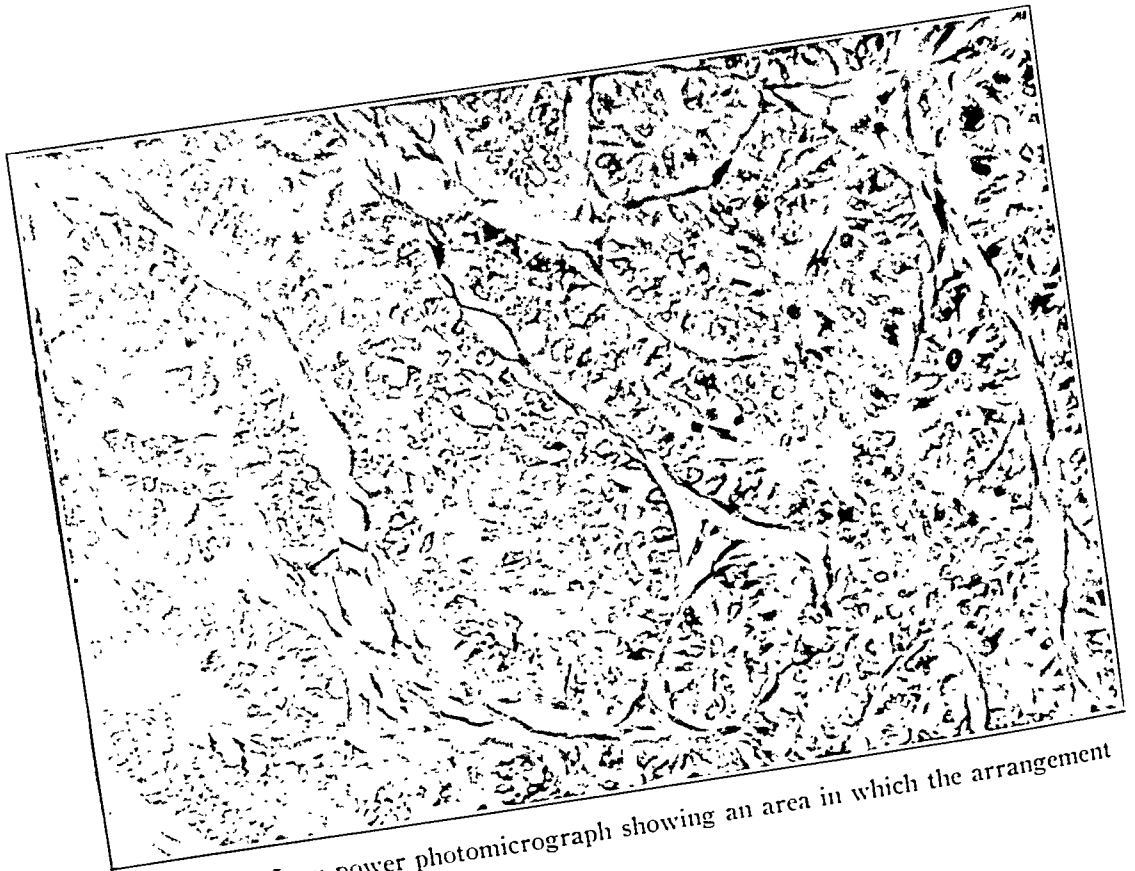


Fig. 7.—Low power photomicrograph showing an area in which the arrangement simulates gland formation.

on the right side of irregular shape, extending from the back of the ramus of the jaw behind and the coronoid process above, downward and forward nearly to the median line and attached to the inferior maxillary bone. It is somewhat coarsely nodular and projects mostly downward and outward. On the inside of the mouth it projects upward above the natural level of the teeth, outward so far as to push out the cheek and somewhat inward so as to slightly displace the tongue to the opposite side. Within the mouth it is lobulated and covered with mucous membrane. The tumor extends back inside the mouth on to the ramus, but cannot be

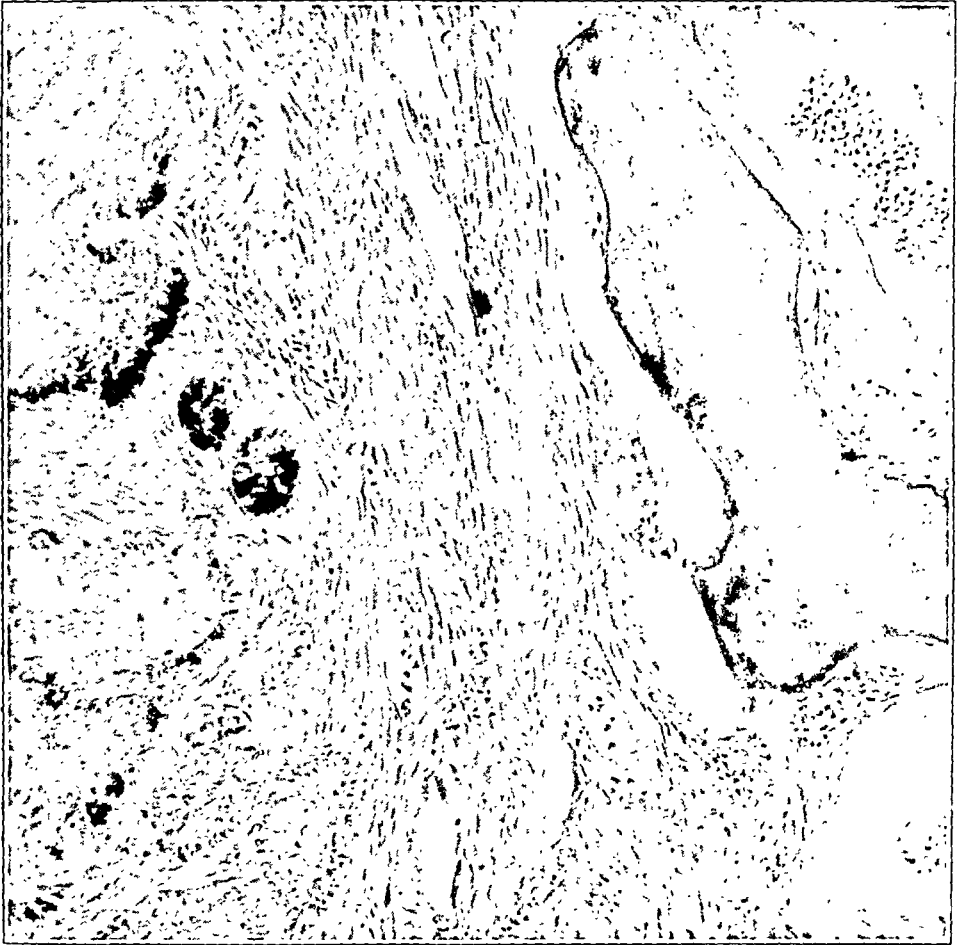


Fig. 8.—Low power photomicrograph showing bone in relation to the tumor.

felt to involve the pharynx at all. The skin over the tumor is not adherent or red. There are no enlarged glands to be felt in the neighborhood and no facial paralysis or dysphagia. There is a constant discharge (worse on lying down), which the patient spits occasionally from the mouth. The discharge comes mostly from two places, posteriorly and anteriorly. Movement of the jaw is not painful."

An operation was performed by Dr. Henry B. Sands<sup>1</sup> on June 23, under ether anesthesia, with antiseptic precautions. The incision was made "from a little below

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1. At this time Dr. Sands was professor of the practice of surgery at the College of Physicians and Surgeons, New York.

and anterior to the external auditory meatus, along lower edge of jaw, 1 inch from midline. Dissection down to tumor, which was very vascular. Bleeding controlled. Canine and first bicuspid teeth extracted. Jaw divided at this point, parts along the floor of the mouth dissected (ether being discontinued) away from the tumor, keeping close to bone; coronoid process dissected out; found to be small and imperfect. Joint dissected out; jaw removed." Seventeen days later, the patient was discharged in good condition, signed out by Dr. George S. Huntington, Senior Assistant Surgeon.<sup>2</sup>

In spite of the radical treatment described, the tumor "soon began to grow" again in the left mandible, and it continued to grow almost up to the time of the patient's death in 1929, when she was 76 years old. Six or eight years before her death the tumor had been treated with radium implantations. For two weeks before death the tumor discharged "foul fluid," and during that time it diminished in size. At all times it had been absolutely, painless.

An incomplete autopsy was performed in the home by Dr. Frank C. Johnson who was called in after the patient's death and obtained the postoperative history from her husband. At this time the mass was removed with what remained of the left mandible. No secondary masses were found in the vicinity, and there was no suggestion of metastases to thoracic or abdominal viscera. Dr. Johnson presented this unusual material to the laboratory.

In the fixed state the specimen consisted of a rounded mass of firm consistency measuring about 11 by 13 by 14 cm. and weighing 950 Gm. (fig. 1). The greater part of its surface was covered with skin. At one end there was a portion of the condyle and ramus of the lower jaw. There were two ulcerated areas on its lower aspect which led into deep cavities. On cut section (fig. 2) irregular masses of bone extended throughout the specimen. Each cut section revealed a vast number of separate cystlike cavities measuring from 1 to 3 cm. in diameter. Cloudy fluid material and débris were found in these cavities. Throughout the specimen between the cystlike cavities there was solid, more or less homogeneous tissue, except for the center of the tumor, which consisted of a mass of extremely friable foul-smelling débris (figs. 3 to 8).

Microscopically, the specimen showed an alveolar-like structure. There were strands of rather densely packed, dark-staining epithelial cells. There were also larger masses of these cells, the more peripheral ones being columnar and arranged radially in a palisade layer. The central cells of the larger masses were less closely packed and lighter staining. Some of them seemed to be connected with bridges, giving them a roughly stellate appearance. In places these central cells were necrotic, with faded nuclei and cloudy cytoplasm. In others, they had disappeared and left small cystic spaces. The strands and masses of epithelial cells were separated from each other by strands of fibrous connective tissue, some of which contained small spicules of well developed bone. The dark-staining epithelial cells and the central stellate cells resembled closely in both appearance and relationship the ameloblasts and the cells of the stellate reticulum of the embryonal enamel organ.

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# LOBECTOMY AND PNEUMECTOMY IN DOGS

## EXPERIMENTAL SURGERY

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AND

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Our interest in experimental lobectomy and pneumectomy was aroused by the discovery of a safe and reliable method of permanently closing large bronchi.<sup>1</sup> A review of the literature on this subject reveals the appalling mortality of these operations to be due primarily to either pleural infection or reopening of the bronchial stump (or both) subsequent to the operation. The idea at once presented itself that these postoperative complications would be obviated by "closing the stump" before removal of the pulmonary tissue. The results of the experimental investigation of this report bear out this hypothesis.

Pneumectomy was first performed by Rolandus<sup>2</sup> (1492) for the cure of diaphragmatic hernia. However, little attention was given to this field of surgery at that time.

At the beginning of the sixteenth century, Schenk<sup>3</sup> aroused interest in thoracic surgery which subsequently has been kindled by the introduction of apparatus and procedures pertaining to this specialty.

Scientific experimental investigation by Gluck,<sup>4</sup> Marcus,<sup>5</sup> Block,<sup>6</sup> Biondi<sup>7</sup> and others was largely a failure as far as the operations per se were concerned. Of these workers, Biondi's results were most encour-

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This work was done in part under a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago.

1. Adams, W. E., and Livingstone, H. M.: Closing Bronchial Stump in Pulmonary Surgery, *Ann. Surg.* **95**:106 (Jan.) 1932.

2. Quoted by Murphy, J. B.: Surgery of the Lung, *J. A. M. A.* **31**:341 (Aug. 13) 1898.

3. Schenk, quoted by Murphy, J. B.: Surgery of the Lung, *J. A. M. A.* **31**:151 (July 23) 1898.

4. Gluck, T.: Experimenteller Beitrag zur Frage der Lungenexstirpation, *Berl. klin. Wchnschr.* **18**:645, 1881.

5. Marcus, quoted by Murphy (footnote 3).

6. Block: Experimentelles zur Lungenresektion, *Deutsche med. Wchnschr.* **7**:634, 1881.

7. Biondi, D.: Lungenexstirpation bei experimenteller lokalisierter Tuberculose, *Med. Jahrb.*, 1884, p. 207.

aging. Using rabbits, cats and dogs, he injected tubercle bacilli into the lungs with the hope of producing localized tuberculous lesions. Eleven subsequent total extirpations of one lung were performed, four of the animals dying of pleural infection. Nevertheless, the experiments carried out were of great value in stimulating interest during that period and led to further experimental and clinical investigation.

Kronlein,<sup>2</sup> in 1884, reported two cases in which the apex of the upper lobe was exteriorized and amputated in the treatment for pulmonary tuberculosis. Both cases terminated fatally.

In 1885, Ruggi<sup>2</sup> operated in two cases with a similar result.

However, Tuffier,<sup>2</sup> in 1891, Lawson,<sup>2</sup> in 1893 and Doyen,<sup>2</sup> in 1895, removed small portions of the apex of the right upper lobe in cases of pulmonary tuberculosis with reported favorable results.

Much subsequent experimental work has been reported, the results of which show marked variation. Thus, Murphy,<sup>8</sup> in 1898, did a partial pneumectomy on ten dogs by the exteriorization and amputation method with a mortality of 90 per cent. However, he expressed his belief that this was the procedure of choice in performing that operation. Previous to Murphy's work there had been no reports of total pneumectomy in man.

Meyer<sup>9</sup> performed total excision of a lung in a series of twenty-one dogs with a mortality of 19 per cent. His method included clamping and crushing of the bronchus with subsequent ligation and amputation and burying of the stump with top sutures.

In the experiments of Lilienthal<sup>10</sup> and Joannides,<sup>11</sup> a generous stump was left for closure. Most workers have found it necessary to leave a liberal amount of lung parenchyma to obtain a satisfactory closure of the bronchial stump following pneumectomy.

Bettman's as well as our own studies on the reparative processes of bronchi<sup>12</sup> have demonstrated little or no healing of the bronchus per se other than regeneration of the epithelium; that healing was brought about by peribronchial tissues. Thus Robinson and Sauerbruch<sup>13</sup>

8. Murphy, J. B.<sup>2</sup>

9. Meyer, Willy: Pneumectomy with the Aid of the Differential Air Pressure, *J. A. M. A.* **53**:1978 (Dec. 11) 1909.

10. Lilienthal, H.: *Thoracic Surgery*, Philadelphia, W. B. Saunders Company, 1926, vol. 2, p. 147.

11. Joannides, Minas: Care of the Stump in Pneumectomy and in Lobectomy, *Arch. Surg.* **17**:91 (July) 1928.

12. Bettman, R. B.: A Study of the Factors Concerned in Failure of the Bronchi to Heal, *Arch. Surg.* **8**:418 (Jan.) 1924. Adams, W. E., and Livingstone, H. M.: Bronchial Injury and Repair, *Ann. Surg.* **91**:342, 1930.

13. Robinson, B. S., and Sauerbruch, F.: Untersuchungen über die Lungen-Exstirpation unter vergleichender Anwendung beider Formen des Druckdifferenz-Verfahrens, *Deutsche Ztschr. f. Chir.* **102**:543, 1909; quoted by Bettman.

found that although removal of a single lobe was almost always successful, the reverse was true following complete extirpation of a lung. With differential pressure, the technic was simple, but many dogs died on the sixth to the eighth day of pressure pneumothorax owing to reopening of the stump. Thirty-eight pneumectomies were performed, in only four of which there was recovery.

The following experimental method is presented because of its simplicity of procedure and its very low mortality.

#### EXPERIMENTAL METHOD

*Preliminary Stenosis of Bronchus.*—Complete stenosis of the bronchus of the lobe or lobes to be removed is obtained prior to operation. This is produced by cauterization of the entire circumference of the bronchial wall by the application

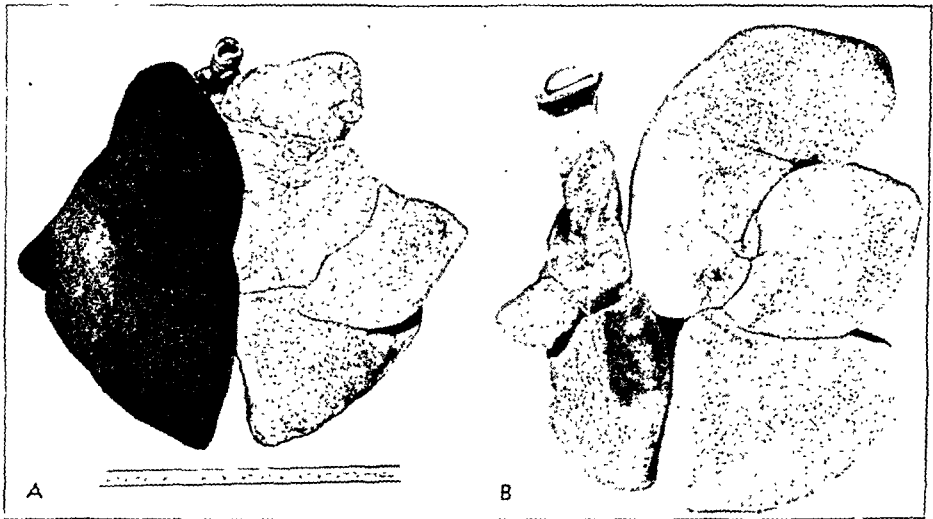


Fig. 1.—*A*, normal lungs showing the relative size of the right and left side. The left lung, shown in black, is collapsed in *B*, and is 100 per cent atelectatic. The right lung in *B* is somewhat hypertrophied.

through a bronchoscope of a 35 per cent solution of silver nitrate. A complete report of this work appears elsewhere.<sup>1</sup> One application usually suffices in bronchi one-half inch (1.27 cm.) or less in diameter. The procedure may be repeated if stenosis is not complete following a single application. The stenosis usually occurs within two weeks following the application of the cautery and is always accompanied by 100 per cent atelectasis of the obstructed pulmonary lobe or lobes (fig. 1, *A* and *B*). When an entire right or left lung is to be removed, the primary bronchus to that side is stenosed.

A diagnosis of complete stenosis of a bronchus, with massive atelectasis of the obstructed lung, is made by endoscopic examination and by the physical findings of dulness to flatness over the side collapsed with the cardiac impulse displaced to that side. These findings are confirmed by fluoroscopic and roentgen examination (figs. 2 and 3).

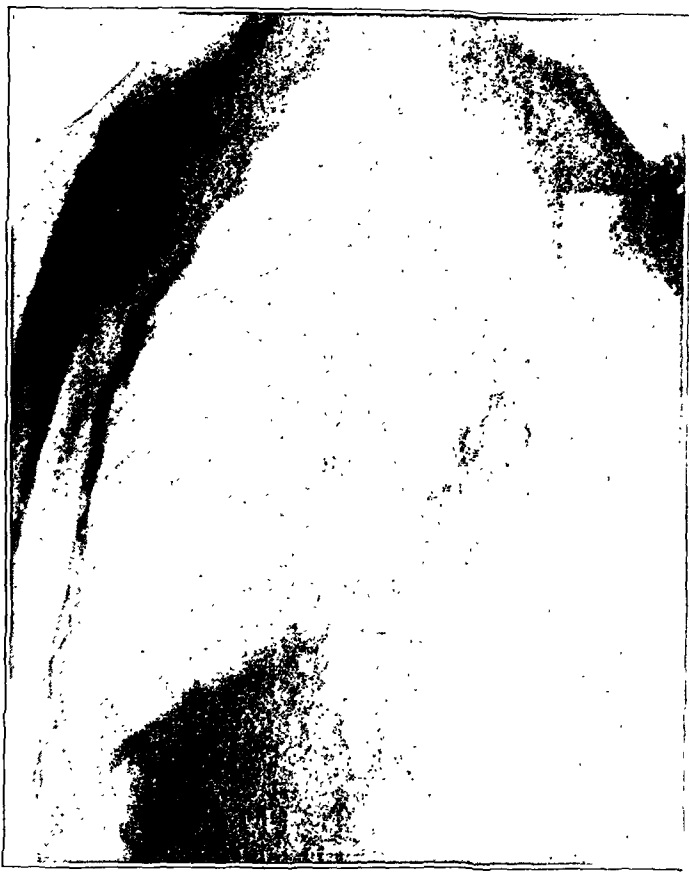


Fig. 2 (dog 837 D).—Roentgenogram of the chest showing massive atelectasis of the left lung following two applications of a 35 per cent solution of silver nitrate to the left primary bronchus. The heart has become displaced and lies against the left thoracic wall. The left side of the diaphragm is also displaced upward.

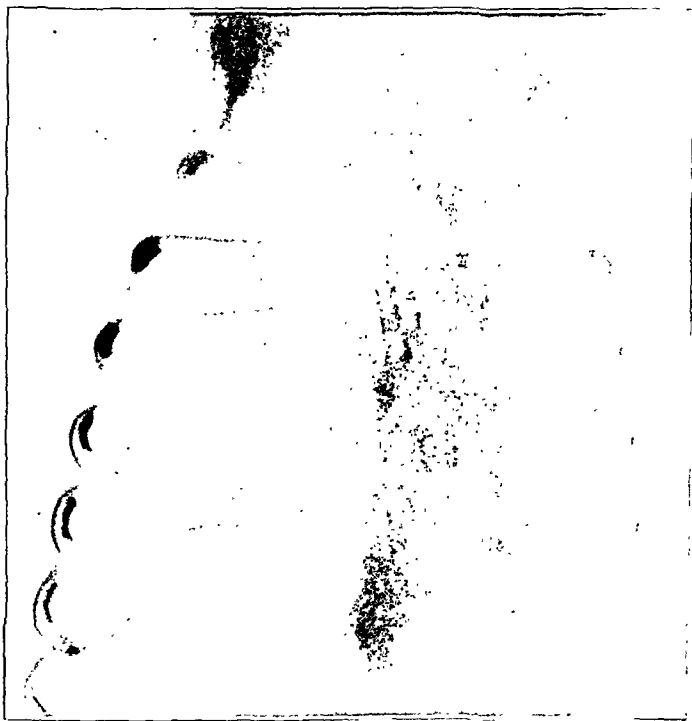


Fig. 3 (dog 400 C).—Roentgenogram of the chest showing massive atelectasis of the right lung. The heart has been displaced against the chest wall and the right side of the diaphragm elevated. Note the dilated bronchi of the remaining inflated lung.



*Removal of Pulmonary Tissue.*—The removal of the pulmonary lobes may be accomplished within a few days to a week subsequent to complete stenosing of the bronchi.

Preliminary to operation, a small dose of morphine and atropine is given. Narcosis is obtained by means of closed ether administration. A complete report by one of us may be found elsewhere.<sup>14</sup> The dog is then placed on the right or left side depending on which pleural cavity is to be entered. The intratracheal tube of the positive pressure ether anesthesia apparatus<sup>14</sup> is now inserted for a depth of 4 or 5 inches (10.16 and 12.7 cm.) into the trachea and the positive pressure mask secured. An air-ether mixture is then administered; however, positive pressure is not yet induced. The thorax is shaved, and the operative field cleansed with tincture of iodine. Sterile drapes are now arranged and careful asepsis observed. An incision 4 or 5 inches in length is made over and paralleling the fifth rib at about its midpoint. About 3 inches (7.6 cm.) of this rib are removed subperiosteally. A small incision is made through the periosteum down to the parietal pleura and the pleural cavity entered bluntly with scissors. The opening is enlarged as the pulmonary lobes become deflated. Positive pressure anesthesia is now begun and regulated so as to obtain only partial inflation of the lungs. With the opening of the pleura, the atelectatic lobes are easily distinguished by their dark bluish-brown color. No pleural exudate is found. The atelectatic lobes are grasped with forceps and mobilized by severing the pleural reflections, following which they are easily lifted up to the surface of the chest. This gives one free access to the vascular supply of the organ. If one entire lung is to be removed, the pulmonary artery to that side is dissected free; two silk ligatures are placed centrally and one distally and the artery is severed between ligatures. If only one pulmonary lobe is to be removed, the pulmonary vessels to that lobe are dissected free, doubly ligated with silk and severed between ligatures. With bleeding thus controlled, the next step consists in isolating each individual lobe bronchus. Each bronchus is dealt with separately in the following manner. A clamp is placed on the bronchus at the edge of the parenchymal tissue, leaving enough space for a chromic catgut ligature proximal to it. This ligature prevents hemorrhage from bronchial vessels. The bronchus is then divided between clamp and ligature. If the division has been made distal to the site of stenosis the air passage will contain a mucogelatinous material, the retained secretion of the bronchial glands. A bare bronchial stump remains, no further care being necessary (figs. 4 and 5).

The wound is now closed in layers under as much positive pressure as is necessary to inflate the remaining lobes to as nearly fill the chest cavity as possible. A running stitch of catgut is used to close the pleura, muscles and subcutaneous tissue. An intracutaneous stitch of catgut is also used preceding closure of the skin by interrupted silk sutures. The wound is dressed and sealed with collodion, and the dog removed to its quarters.

*Postoperative Course.*—During the first two days the animal eats little or nothing and appears somewhat weak. It lies quietly in its cage most of the time. By the third or fourth day, however, it is up and walking about a great deal. It eats well and appears to be gaining strength quite rapidly. At the end of a week, it appears entirely well. Most dogs exhibited a nonproductive cough during the first four or five days following operation. All of the wounds closed in the described manner, remained clean and healed by primary union.

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14. Livingstone, H. M., and Hrdina, L. S.: A Modified Meltzer Apparatus for Anaesthesia in Animals, *J. Lab. & Clin. Med.* **16**:74, 1930, fig. 3.



Fig. 4.—*A* and *B*, views of the heart and left lung of a dog killed following pneumectomy of the right lung. View *B* shows the bronchial stump remaining after pneumectomy.

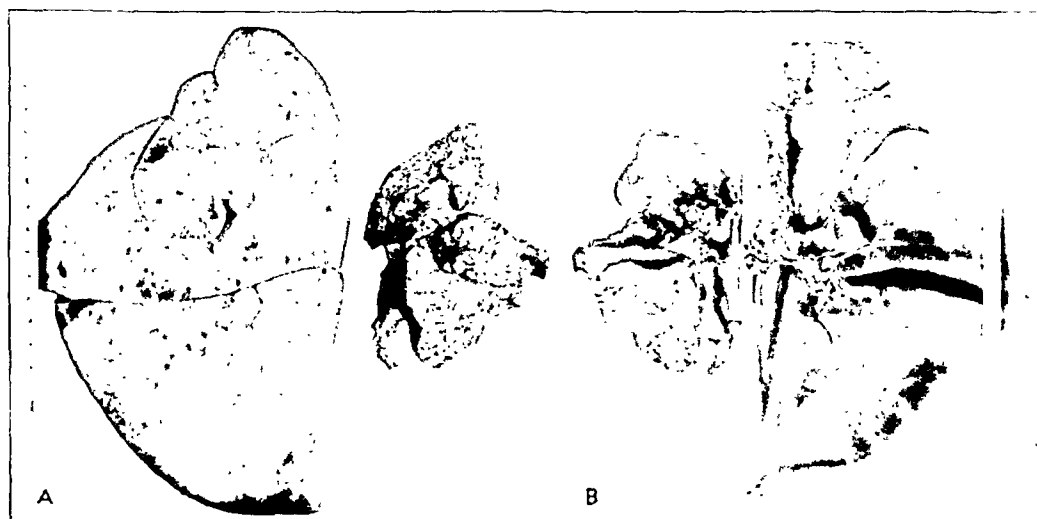


Fig. 5.—*A* and *B*, views of the lungs. The small atelectatic right lung was removed at operation. Note the contrast in size and color to the larger left lung which was removed at time of autopsy. *B* shows the bronchial stump remaining after pneumectomy of the right lung.

## RESULTS

One or two lobes were removed in twenty dogs without a single death. All pulmonary lobes on one side were extirpated in eight dogs with the death of one animal. This dog died of respiratory failure on the operating table as the operation was completed, due to defective tubing in the positive pressure apparatus. A careful preoperative check of the apparatus would have obviated this accident. Of the remaining



Fig. 6 (dog 795 C).—Roentgenogram of the chest taken six months following the removal of the right lower and accessory pulmonary lobes, and three weeks following pneumectomy of the left lung. Note the heart and trachea drawn far to the left with elevation of the left side of the diaphragm. The remaining two right lobes exhibit compensatory emphysema, being hyperinflated to fill the thoracic cavity.

seven, two have had a subsequent lobectomy performed on the opposite side, two lobes being removed in each dog. Both dogs had an uneventful convalescence. Thus a total of thirty operations have been performed on twenty-eight dogs without a single death due to the procedures per se (fig. 6). Dogs killed from two months to a year following the foregoing procedures presented no fluid in the pleural cavities. A small number

of adhesions were found in the region of the amputation stump. The remaining pulmonary tissue exhibited varying degrees of compensatory emphysema (fig. 7). Electrocardiograms prior to the death of the animals deviated very little from the normal.

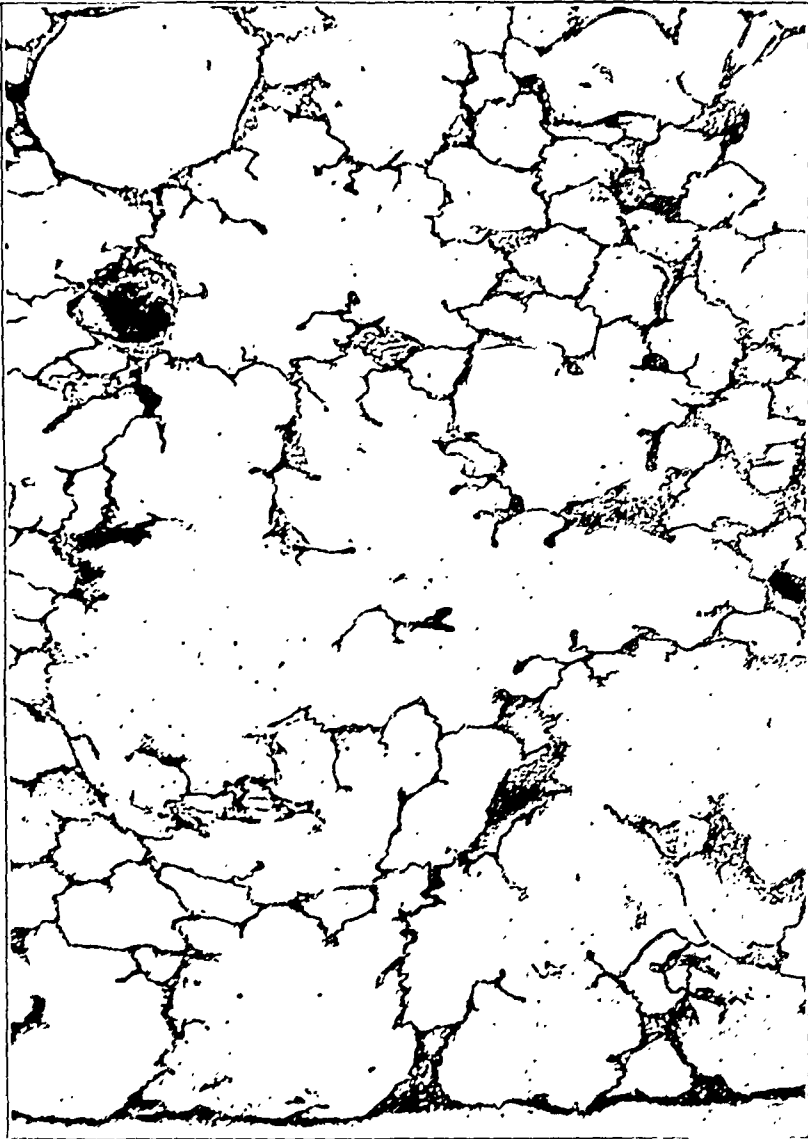


Fig. 7.—Photomicrograph of inflated pulmonary tissue of a dog killed several months subsequent to pneumectomy of an atelectatic right lung, showing marked emphysema.

#### COMMENT

The preliminary production of a complete stenosis of the pulmonary lobe bronchus preceding lobectomy was simple and accompanied by no mortality when a solution of silver nitrate of 35 per cent or less was employed. By using this procedure, danger of pleural infection or

pneumothorax following the subsequent amputation of the pulmonary lobes was obviated, an air-tight closure of the bronchial stump having been produced prior to removal of the pulmonary lobe. Thus, there is no dependence on popostoperative healing to produce an air-tight closure of the bronchial stump as is the case in operations in which the stump is closed subsequent to removal of the pulmonary tissue. Postoperative pleural infection and pneumothorax having thus been obviated, the mortality accompanying the procedure was practically nil.

No postoperative complications arose due to reopening of a stenosed bronchial lumen.

During the operation, hemostasis was readily obtained, and the pulmonary lobes were easily removed owing to their having shrunk down to the atelectatic condition. Complete pneumectomies were performed in from twenty to thirty minutes, and the subsequent removal of a lobe on the opposite side was accompanied with equal ease and success.

This procedure is being made use of at the present time in studies on the cardiorespiratory physiology of bilateral subtotal pneumectomized dogs.

Preparations are being made to test its clinical application.

#### CONCLUSIONS

The simplicity of preparation and execution and the exceedingly low associated mortality are the remarkable features of this operation.

It has proved highly satisfactory in experimental investigations; however, its clinical application is yet to be demonstrated.

The usual difficulties of associated pneumothorax and pleural infection have been obviated, and thus the greatest obstacles in performing pneumectomy have been overcome.

#### PROTOCOL

Dog 795 C.—The dog weighed 11.5 Kg. Complete stenosis of the right lower and accessory lobe bronchi was produced. This was accompanied by massive atelectasis of these two lobes. The removal of these two lobes was carried out a few weeks later. Three months subsequent to this the left primary bronchus was completely stenosed and the left lung collapsed. Pneumectomy of the left lung was performed several months later. The dog is healthy and active at the present time, four months following the last operation; 23.7 per cent of the original pulmonary tissue remains.

July 3, 1930: The dog was given a prebronchoscopic dose of morphine of  $\frac{1}{4}$  grain (16 mg.) per kilogram of body weight. One and one-half hours later, bronchoscopy was performed and the right accessory lobe bronchus cauterized with a 35 per cent solution of silver nitrate. The dog was quiet for a few days and exhibited a nonproductive cough.

July 15: Bronchoscopy was carried out as described. The accessory lobe bronchus was completely stenosed. The right lower lobe bronchus was cauterized with a 35 per cent solution of silver nitrate. A postbronchoscopic course similar to that described, followed.

August 22: Bronchoscopy revealed complete stenosis of the right lower lobe bronchus.

August 26: Lobectomy of the right lower and accessory lobe bronchi was performed.

A preoperative dose of morphine, 0.015 Gm., and atropine, 0.0004 Gm., was given. Under intratracheal ether anesthesia, an incision was made over and paralleling the right sixth rib. The right pleural cavity was entered bluntly through the fifth interspace and positive pressure anesthesia begun as the thoracic contents fell away from the chest wall. The atelectatic lobes (right lower and accessory) were easily recognized by their color. The branch of the pulmonary artery to the right lower lobe was dissected free, two ligatures of silk placed centrally and one distally and the artery divided between ligatures. This also cut off the blood supply to the accessory lobe. The several veins leading from the two lobes to the left auricle were dealt with in a similar manner. The bronchus of each lobe was clamped individually, just proximal to the lung parenchyma. A silk ligature was placed proximal to the clamp to control bleeding of the bronchial vessels and the bronchi each divided between clamp and ligature. As the bronchi were divided, a mucogelatinous material was seen signifying that the division was distal to the site of stenosis. No further care was given the bronchial stump. The remaining lung tissue was inflated by increasing the positive pressure so that the entire thoracic cavity was filled by its contents. The wound was closed in layers under positive pressure, using heavy braided silk to retain the fifth and sixth ribs in close approximation. Catgut was used for the muscle and subcutaneous tissues, an intracutaneous suture of catgut also being used. The skin was closed with interrupted silk and a collodion dressing applied. The dog was returned to its quarters in good condition.

August 27: The dog lay quietly in its quarters and refused food. An occasional nonproductive cough was exhibited.

August 29: The dog walked about and appeared to be improving.

August 31: The dog appeared entirely well except for an occasional nonproductive cough. The wound had healed by primary intention.

October 9: Bronchoscopy was performed. The right lower and accessory lobe bronchi appeared as before. The left primary bronchus was cauterized with a 35 per cent solution of silver nitrate. The usual postbronchoscopic course followed.

October 29: Bronchoscopy was carried out as previously described. The left primary bronchus was completely stenosed. On physical examination, the left side of the chest was flat to percussion. Fluoroscopy and roentgen examination disclosed the heart drawn against the left thoracic wall and massive atelectasis of the left lung.

April 23: Pneumectomy of the left lung was performed. A preoperative dose of morphine, 0.015 Gm., and atropine, 0.0004 Gm., was given.

Under intratracheal ether anesthesia an incision was made over the left fifth rib, and 3 inches of this rib was removed subperiosteally. The left pleural cavity was entered bluntly and positive pressure anesthesia begun as the thoracic contents fell away from the wound. The heart was found to lie directly beneath the incision, and the left lung was 100 per cent atelectatic. The left pulmonary artery was

dissected free, two ligatures placed centrally and one distally and the artery severed between ligatures. The several veins leading from the two lobes were dealt with in like manner. The left upper lobe bronchus was clamped near the parenchyma of the lobe, and a ligature was placed proximal to the clamp to control bronchial bleeding. The bronchus was divided between clamp and ligature. The left lower lobe bronchus was treated in a similar manner.

The remaining lung was inflated by increasing the positive pressure so that almost the entire thoracic cavity was filled by its contents.

The wound was closed in layers under positive pressure and a dressing applied.

April 24: The dog lay quietly in its quarters and refused food. An occasional nonproductive cough was exhibited.

April 26: The dog appeared to be improving. It walked about and took both food and water.

April 28: The dog appeared entirely well except for an occasional nonproductive cough. It was quite active. The wound had healed by first intention.

May 3: The dog appeared normal. No cough had been present during the past two days.

## INTERNAL HERNIA

### THREE ADDITIONAL CASE REPORTS

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AKRON, OHIO

The subject of internal hernia is one that surgical textbooks have largely neglected. Although Watson, in his volume on hernia, devoted a chapter to the subject, and H. B. Stone also mentioned internal hernias in some detail, in many instances but little attention is paid them. They are comparatively rare, but for that very reason are important since their rarity makes their diagnosis difficult.

By the term internal hernia is meant a protrusion into pouches or openings in the peritoneum in contrast to hernias through defects in the retaining walls of the abdomen. There are many varieties. Watson classed as most common those of the duodenal fossae described by Eppinger, Treitz and Landzert: the pericecal, the intersigmoid and those through the foramen of Winslow. Stone said that the most frequent are those about the duodenojejunal junction: the cecum, the mesentery of the sigmoid and through the foramen of Winslow.

Short gave seven common types of internal hernia: the left and right paraduodenal, the retrocolic, the ileo-appendicular, those through the foramen of Winslow, the intersigmoid and those through the transverse mesocolon. The eleven other cases given are in locations too infrequent to deserve separate classification. Stangl divided retroperitoneal hernia into duodenal, pericecal, intersigmoid and hernia through the foramen of Winslow. This is a classification with which Lower and Higgins agree.

The classification of internal hernia is not, as a matter of fact, without confusion. In looking over the literature it is found that some authors use the term retroperitoneal hernia without further division. This use is too general, for the term retroperitoneal hernia covers a large field and includes many of the internal hernias. Others use this term interchangeably for the hernia of Treitz, a classification that Short does not use. No doubt he placed this type of hernia in the paraduodenal group, since the fossa occurs just at the end of the duodenum. Garber uses the term interchangeably for the duodenojejunal variety. His cases have been classed under hernia of Treitz. Watson, however, listed duodenojejunal hernia as a separate class and wrote that it is



rarely associated with any other variety of duodenal fossa. It is exposed by pulling the transverse colon upward and the jejunum downward and to the right.

To a large extent the classification of Short has been adhered to in this paper. This has simplified comparison of reports of internal hernia in the literature from 1925 to July, 1931 (the period covered here), with those reported by him in 1925. The cases of hernia of Treitz, classed definitely by the authors under this heading, should be placed under the paraduodenal group. In addition, space has been given for recording unclassified retroperitoneal hernias, for duodenojejunal hernias and for paraduodenal hernias in which the side involved is not stated.

It is my opinion that the best classification of retroperitoneal hernia is paraduodenal (right and left and duodenojejunal groups), paracecal, intersigmoid and hernia through the foramen of Winslow. Internal hernias should include this group of retroperitoneal hernias, together with hernias into anomalous openings, such as, through the mesentery (transverse mesocolon, etc.), through the omentum and into or through the broad ligament.

*Classification of Internal Hernias*

Retroperitoneal											
Paraduodenal	<table> <tr> <td>{</td><td>Right</td></tr> <tr> <td>{</td><td>Left</td></tr> <tr> <td>{</td><td>Duodenojejunal</td></tr> <tr> <td></td><td>Superior</td></tr> <tr> <td></td><td>Inferior</td></tr> </table>	{	Right	{	Left	{	Duodenojejunal		Superior		Inferior
{	Right										
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	Superior										
	Inferior										
Paracecal	<table> <tr> <td>{</td><td>Ileocecal</td></tr> <tr> <td>{</td><td>Retrocecal</td></tr> <tr> <td>{</td><td>Ileocolic</td></tr> </table>	{	Ileocecal	{	Retrocecal	{	Ileocolic				
{	Ileocecal										
{	Retrocecal										
{	Ileocolic										
Intersigmoid											
Foramen of Winslow											
Anomalous openings											
	Through the mesentery										
	Through the omentum										
	Through or into the broad ligament										

In 1925, Short reviewed the literature on internal hernia, bringing the case reports up to date. While no attempt has been made to cover the same ground, and only cases reported in the American, English, German and French literature have been looked up, yet in the course of this search certain omissions to his bibliography have been discovered. Thus Short, reporting the case of Copenhagen of internal hernia through the foramen of Winslow, omitted from his summary the ileocecal hernia and the hernia through the omentum, both of which are given in the same paper. The case of Bryan of duodenojejunal hernia is not reported. He mentioned Andrew's article but did not include the case of paraduodenal hernia reported there. Nor did he give the case of Ullman, nor Radovan's case which Ullman quotes.

Other authors have also reported cases that he missed. The case of Pringle of a girl 5 years old, the case of Coffey, the case of Crymble—all reported by Heaney and Simpson—are not included in Short's paper. Dewis and Miller, in their discussion of hernia through the foramen of Winslow, noted several cases that Short missed. Garber reported two cases of hernia of Treitz, reported since Short's paper, but not included in my bibliography. All these cases are given in table 1.

TABLE 1.—Cases Omitted by Short

Author	Type of Hernia	Result
Quoted by Dewis and Miller:		
Delangenier, 1924.....	1 through foramen of Winslow	Not given
Corry, 1924.....	1 through foramen of Winslow	Reduction with recovery
Ullman, 1924.....	1 through foramen of Winslow	Enterotomy with death
quotes Radovan, 1919.....	1 through foramen of Winslow	Enterotomy with recovery
Garber quotes:		
Kuschewa and Malenowsky	1 hernia of Treitz	Not given
Jefeth.....	1 hernia of Treitz	Not given
Heaney and Simpson quote:		
Pringle.....	1 through transverse mesocolon	Not given
Coffey.....	1 through transverse mesocolon	Not given
Crymble.....	1 through transverse mesocolon	Not given
Copenhaver, 1923.....	1 ileocecal	Enterostomy with death
	1 through omentum	Resection with death
Andrews, 1923.....	1 paraduodenal	Hole sutured; result not given
Bryan, 1920.....	1 duodenojejunal	Reduction; enterojejunostomy recovery

TABLE 2.—Total Number of Cases of Internal Hernia

Type of Hernia	Short 1915-1925	Omitted by Short	1925-1931	Total
Retroperitoneal unclassified.....	..	..	2	2
Paraduodenal				
Duodenojejunal.....	..	1	3	4
Treitz.....	..	2	6	8
Side unstated.....	..	1	1	2
Left.....	43	..	5	48
Right.....	5	..	4	9
Paracecal )				
Retrocolic.....	17	..	4	21
Ileo-appendicular.....	5	1	2	8
Foramen of Winslow.....	24	4	7	35
Intersigmoid.....	8	..	4	12
Through transverse mesocolon.....	17	3	8	28
Others.....	11	1	14	26
Totals.....	130	13	60	203

In this paper fifty-seven more cases have been culled from the literature, and 3 personal cases are reported. This brings the total up to two hundred and three. In table 2 these have been summarized according to the location of the hernia, and added to previous total reported cases.

## REPORT OF CASES

The three cases from my personal record are given here.

CASE 1.—H. D., a man, aged 43, was seen with acute pain in the upper abdominal region, shock and vomiting approaching the fecal type. The previous history elicited stabbing pain in the epigastrium and upper left side of the abdomen.

associated with vomiting. These attacks lasted from two to three days and were preceded by attacks of constipation. The symptoms were of four years' duration, with attacks becoming more frequent. General examination revealed a well built and well nourished man. The abdomen was of the semibarrel type. There was no visible or palpable mass on pulsation. There was slight tenderness in the epigastrium and gas distention. The preoperative diagnosis was intestinal obstruction or pancreatitis. Operation, with the patient under ethylene and ether, revealed a membranous pocket extending from mesenteric attachment of the vertebra to the left side of the abdominal wall, producing a pouch of the left paraduodenal type with opening  $1\frac{1}{2}$  inch in diameter. This pouch contained all the jejunum and 6 feet of the ileum. About 6 ounces of serosanguineous fluid escaped. The intestines were removed from the pouch, and the membranous band was incised, the hernial sac being destroyed. The recovery was good. The appendix had been removed previously.

CASE 2.—B. X., a woman, aged 29, gave a history of bloating and much gas after meals, especially after eating beans. Appendectomy had been performed several weeks before by another surgeon without relief. No doubt the hernia was overlooked at this operation. There was no vomiting. Her physician gave her castor oil, and she had a dozen small bowel movements. Examination revealed a bulge to the left of the umbilicus the size of a grapefruit. Peristalsis was normal. The preoperative diagnosis was abdominal tumor.

At operation the small intestine was not visible free in the abdomen, and it was observed under the peritoneum. The greater part of the small bowel had herniated through an opening into a pouch, causing partial obstruction. There was some lymph exudate at the cecal region, and all the small intestines were highly congested after delivery from the sac. The hernia was of the left paraduodenal type. The peritoneal holes were sutured, and the patient went into shock. The incision was closed. There was a gradual recovery.

Eleven years later the patient was seen for lacerated cervix and perineum, retroversion of the uterus with some prolapsus. In the course of operation the small intestine was found matted together with many adhesions. The omentum was free, but the bowel was adherent to the upper end of the incision. The bladder was adherent to the uterus. The region of the former hernial opening was found to be closed and covered with scar tissue. The upper portion of the abdomen was completely sealed off with adhesions. Recovery was good.

CASE 3.—A. Z., a man, aged 26, had undergone posterior gastro-enterostomy, performed three weeks previously for duodenal ulcer by another surgeon. For two weeks the patient vomited green material and suffered from pain and colic. The preoperative diagnosis was vicious circle or obstruction. Operation revealed the small bowel in the lesser peritoneal cavity, through the transverse mesocolon where it had not been fixed to the stomach. The hernia was reduced and the opening sutured. Good recovery followed.

#### REVIEW OF LITERATURE

The sixty cases of internal hernia reported since 1925, including the foregoing three cases, up until July, 1931, are listed in table 3 alphabetically according to the author and the type of hernia. The totals at the bottom of this table correspond to the totals in the third column in table 2.

In table 4 the cases are again listed alphabetically according to authors, and further data: sex, age, symptoms, type of operation, result, etc., have been tabulated.

TABLE 3.—*Classification of Cases of Internal Hernia Reported Since 1925*

Author	Retroperitoneal Unclassified	Paraduodenal					Paracecal	Foramen Of Winslow	Intersig- moid	Through Mesentery		Others
		Duodeno- jejunal	Hernia of Treitz	Side Not Stated	Left	Right				Through Mesocolon	Location Not Stated	
Algrot, 1930.....	..	..	..	..	..	..	..	1	..	..	..	
Brown, 1929.....	..	1	..	..	..	..	..	..	..	..	1	
Cabot, 1927.....	..	..	..	..	..	..	..	1	..	..	..	
Carling, 1926.....	..	..	..	..	..	..	..	1	..	..	..	
Christophe, 1926.....	..	..	2	..	..	..	..	..	..	..	..	
Coley and Hoguet, 1929..	..	..	..	..	..	1	1	..	..	..	..	
Deaver and Burden, 1929..	..	..	..	..	..	..	1	..	..	..	..	
Debray, 1929.....	..	..	1	..	..	..	..	..	..	..	..	
Dewis and Miller, 1927....	..	..	..	..	..	..	1	1	..	..	..	
Donald, 1930.....	..	..	..	..	..	..	1	..	..	..	..	
Eitel, 1926.....	..	..	..	..	1	..	..	..	..	..	..	
Elston, 1926.....	..	..	..	..	..	..	..	..	..	..	1	
Erdély, 1927.....	..	1	..	..	..	..	..	..	..	..	..	
Folliasson, 1931.....	..	..	1	..	..	..	..	..	..	..	..	
Garher, 1928.....	..	..	1	..	..	..	..	..	..	..	..	
Gibby, 1928.....	..	..	..	..	..	..	..	..	1	..	..	
Godard and Smith, 1929...	..	..	..	..	..	..	..	..	..	1	..	
Green, 1927.....	..	..	..	..	..	..	..	1	..	..	..	
Hamilton, 1926.....	..	..	..	..	..	..	..	..	1	..	..	
Heaney and Simpson, 1925..	..	..	..	..	..	..	..	..	..	2	..	
Hennig, 1926.....	..	..	..	..	..	..	1	..	..	..	..	
Jackson, 1930.....	..	..	..	..	..	..	..	1	..	..	..	
Janes, 1929.....	..	..	..	..	..	..	..	..	..	..	..	2 broad ligament
Judd, 1929.....	..	..	..	..	..	..	..	..	..	..	1	
Koch, 1926.....	..	..	..	..	..	..	..	..	..	1	..	
Kostić, 1927.....	..	..	..	..	..	..	..	..	1	..	..	
Lefèvre, 1927.....	..	..	..	..	..	..	..	..	..	1	..	
Liebers, 1926.....	..	..	1	..	..	..	..	..	..	..	..	
Long, 1929.....	1	..	..	..	..	..	1	..	..	..	..	
Lower and Higgins, 1925..	..	..	..	..	1	1	..	..	..	..	..	
Malcomb, 1927.....	..	1	..	..	..	..	1	..	..	..	..	
Martzloff, 1930.....	..	..	..	..	..	..	..	..	..	..	..	1 omentum
Masson, 1930.....	..	..	..	..	..	1	..	..	..	..	..	
McCarthy, 1926.....	..	..	..	..	..	..	..	..	1	..	..	
Muller, 1928.....	..	..	..	..	..	..	..	..	..	..	1	
Nel, 1929.....	..	..	..	..	..	..	..	..	..	1	..	
Odermatt, 1926.....	..	..	..	..	..	..	..	..	..	1	..	
Siegmund, 1927.....	..	..	..	..	..	..	..	..	..	3	..	
Stangl, 1930.....	..	..	1	..	..	..	..	..	..	..	..	
Steinke, 1931.....	..	..	..	..	2	..	..	..	..	1	..	
Sumner, 1929.....	1	..	..	..	..	..	..	..	..	..	..	
Thevenard, 1928.....	..	..	..	..	..	..	..	1	..	..	..	
Traum, 1931.....	..	..	..	..	..	..	1	..	..	..	..	
Turner and Scholefield, 1930.....	..	..	..	..	1	..	..	..	..	..	..	
Venables, 1930.....	..	..	..	..	..	1	..	..	..	..	..	
Vidgoff and Stureon, 1930..	..	..	..	..	..	..	1	..	..	..	..	
Watschugoff, 1931.....	..	..	..	..	..	..	..	..	..	..	..	3 fovea supra- vesicalis
Total, 60.....	2	3	6	1	5	4	7	7	4	11	4 6	

In table 5 is compared the mortality of the cases listed from 1925 to 1931 with the mortality given by Short.

From these tables and the material from which they are drawn certain interesting facts come to light.

TABLE 4.—Cases of Internal Hernia Reported Since 1925

Author	Sex	Age	Symptoms	Preoperative Diagnosis	Operation	Type of Hernia	Results	Comment
Alkrot, 1930.....	M	67	Stomach trouble for 20 yrs.; acute pain in epigastrium; vomiting for 24 hrs.	Perforated ulcer of stomach	Reduction	Foramen of Winslow	Recovery	
Brown, 1923.....	..	..	Symptoms of obstruction; abdominal pain; vomiting	Acute intestinal obstruction	Reduction; jejunotomy	Duodeno-jejunal through mesentery	Recovery	Two operations
Cabot, 1927.....	M	30	Acute abdominal pain; collapse	Diffuse peritonitis; obstruction	Reduction	Foramen of Winslow	Recovery	
Carling, 1926.....	M	27	Acute abdominal pain	Gastric ulcer	Reduction; duodenojejunostomy	Treitz	Death	Hernia not recognized at first operation; death from laryngitis
Christophe, 1926.....	M	37	Gastric symptoms for 5 yrs.; colic, vomiting, tumor for 6 wks.	Not made	Celiotomy	Treitz	Death	Autopsy showed hernia
Coley and Hogue, 1926.....	M	63	Symptoms of intestinal obstruction	Not made	Reduction	Retrocolic	Recovery	Roentgenogram negative
Debray, 1929.....	M	39	Occasional abdominal pain for 6 mos.	Retroperitoneal	Reduction	Foramen of Winslow	Recovery	
Devenor and Burden, 1929 (a)	M	27	Sudden onset; pain in upper portion of abdomen; vomiting, gastric symptoms several years	Not made	Reduction	Right paraduodenal	Recovery	
Devenor and Burden, 1929 (b)	M	25	Severe pain in abdomen; vomiting previous attacks	Subsiding appendicitis	None	Treitz	Death	Autopsy showed hernia
Debray, 1929.....	F	63	History of alternate diarrhea and constipation; vomiting	Terminal generalized peritonitis	"Tumor" found and drained	Foramen of Winslow	Death	Autopsy showed hernia
Devis and Miller, 1927....	F	42	Pain in epigastrium for 20 days; another attack 2 wks.; vomiting	Perforated peptic ulcer of cholecystitis	Reduction	Paracecal	Death	Death 2 hrs. after operation
Donald, 1930.....	M	57	Abdominal pain for 4 days; vomiting	Acute obstruction	Reduction; jejunostomy	Left paraduodenal through mesentery	Recovery	
Eltel, 1926.....	M	..	Digestive disturbances for years	Acute appendicitis	End-to-end anastomosis	Duodeno-jejunal	Recovery	Reduction impossible; congenital aperture
Elston, 1926.....	F	16	Sudden onset of abdominal pain, nausea, vomiting; previous attack 4 mos. ago	Not made	Reduction		Recovery	
Erddly, 1927.....	M	31	Fever, constipation, vomiting, cramps for 8 mos.; tumor-like mass for 3 wks.	Hernia				

Folliasson, 1931.....	M	21	Nausea, vomiting, gastric distress; symptoms of obstruction	Obstruction; tuberculosis?	Reduction	Treitz	Recovery	Roentgenogram showed obstruction
Garber, 1923.....	M	62	Severe pain in abdomen; similar attacks 20 yrs.; swelling on left side	Mesenterial cyst	Reduction	Treitz	Recovery	.....
Gibby, 1923.....	M	37	Sausage-like mass on left side for 2 yrs.; pain for 2 wks.	Probable retro-peritoneal sarcoma	Reduction	Intersigmoid	Recovery	Roentgenogram showed obstruction
Godard and Smith, 1929	..	..	Subacute gastric symptoms	Duodenal stasis	(1) Gastro-enterostomy; (2) reduction	Transverse mesocolon	Recovery	Roentgenogram showed duodenal stasis; hernia not diagnosed first operation
Green, 1927.....	M	42	Occasional gastric disturbance; pain in abdomen; vomiting; constipation	Not made	Enterotomy reduction	Foramen of Winslow	Death	.....
Hamilton, 1926.....	..	..	Colicky pain; vomiting for 6 wks.	Intestinal obstruction	Reduction	Intersigmoid	Death	Death due to aneurysm on 19th day
Heaney and Simpson 1925	F	52	Chronic gastric symptoms; occasional vomiting; 12 mos. previously acute pain in stomach	Tumor	Gastro-enterostomy	Transverse mesocolon	Recovery	Hour-glass stomach
(b)	F	38	Gastric disturbance for 16 yrs.; gastric hemorrhage 18 mos. ago; vomiting; pain for 6 wks.		Reduction; stomach resected	Transverse mesocolon	Recovery	Roentgenogram showed hour-glass stomach
Hennig, 1926.....	F	16	Chronic abdominal pain; acute for 24 hrs.	Ovarian tumor	End-to-end anastomosis	Retrocolic	Recovery	.....
Jackson, 1930.....	..	..	Digestive disturbances	Hernia	Reduction	Foramen of Winslow	Recovery	Diagnosis by roentgenogram
Janes, 1929.....	F	58	Repeated attacks of abdominal pain for 10 mos.; last attack of pain with distention	Cyst	Reduction	Left broad ligament	Recovery	.....
(b)	F	36	Abdominal pain, cramps, vomiting; one previous attack	Not made	Exploratory	Left broad ligament	Death	Death due to cardiac failure; autopsy showed hernia
Judd, 1929.....	M	10	Abdominal pain, vomiting for 3 days	Obstruction	Reduction	Through mesentery	Recovery	.....
Koch, 1926.....	F	15	Severe abdominal pain for 3 days	Ovarian cyst	Reduction	Transverse mesocolon	Recovery	.....
Kostić, 1927.....	M	33	Colicky pains, vomiting; onset sudden	Intestinal obstruction	Reduction	Intersigmoid	Recovery	.....

TABLE 4.—Cases of Internal Hernia Reported Since 1925—Continued

Author	Sex	Age	Symptoms	Preoperative Diagnosis	Operation	Type of Hernia	Results	Comment
Leclerc, 1927.....	M	44	Symptoms typical pyloric stenosis; chronic gastric symptoms	Pyloric stenosis	Gastro- enterostomy	Transverse mesocolon (congenital)	Recovery	Diagnosis by roentgenogram
Liebers, 1926.....	..	..	.....	.....	.....	Treitz	Death	Died of military tuberculosis; hernia at autopsy
Long, 1929.....	M	51	Cramp-like pains, vomiting	Obstruction	Reduction	Retro-peritoneal	Recovery	.....
	M	24	Abdominal pain, colic, nausea	Not given	Reduction	Retrocolic	Recovery	.....
Lower and Higgins, 1925	F	13	Abdominal distention, vomiting for 9 wks.	Intestinal obstruction	Reduction	Right para-duodenal	Recovery	.....
	M	50	Abdominal distention, pain, nausea, constipation; mass in region of cecum for 2 yrs.	Tumor of cecum	Reduction impossible	Left para-duodenal	Recovery	.....
Malcomb, 1927.....	M	22	Sudden pain, vomiting, prostration	Intestinal obstruction	Reduction	Duodeno-jejunal	Recovery	.....
	M	18	Sudden abdominal pain, vomiting; similar attack 3 yrs. ago	Acute appendicitis	Reduction	Ileo-appendicular	Recovery	.....
Martziolf, 1930.....	F	24	Gas, epigastric fullness several years; acute discomfort, nausea, vomiting for 7 days	Pyelitis; possible appendicitis	Reduction	Through omentum	Recovery	.....
Masson, 1930.....	..	..	Epigastric pain for 12 yrs.; bloating, vomiting	Probable cholecystitis; obstruction	Reduction; resection ileum	Right para-duodenal	Recovery	.....
McCarthy, 1926.....	M	20	Extreme shock; severe abdominal pain; nausea, marked tetanus; sudden onset	Ruptured appendix; perforated intestinal ulcer	Resection impossible; all small; part large bowel gangrenous	Intersigmoid	Death	Diagnosis not made until 18 hours after onset
Muller, 1928.....	M	39	Sudden abdominal pain; vague symptoms for 10 to 15 yrs.; constipation alternated with diarrhea	Gangrenous appendix	None	Through mesentery	Death	Died before operation was possible
Nel, 1929.....	F	..	Acute abdominal pain; vomiting; collapse	Perforated gastric ulcer	Reduction	Through transverse mesocolon	Recovery	Possible cause—fall from horse

Odermatt, 1926.....	F	68	Abdominal distress for 3 yrs.; loss of weight; vomiting	Intestinal cancer	None	Through transverse mesocolon	Death	Condition too bad for operation
Slegmund, 1927.....	M	18	.....	.....	None	Under mesocolon	Death	Autopsy, died of grip
	F	32	.....	.....	None	Under mesocolon	Death	Autopsy, died of angiodysplasia
	M	74	Symptoms intestinal obstruction for 20 yrs.	.....	None	In meso-sigmoid	Death	Autopsy, died of appendicitis
Stangl, 1930.....	..	..	No symptoms of obstruction	Bullet wound	None	Para-duodenal	Death	Hernia at autopsy
Steinke, 1931.....	M	43	Acute abdominal pain; shock; vomiting; pancreatic symptoms; abdominal pain for 4 yrs.	Intestinal obstruction; pancreatitis	Reduction	Left para-duodenal	Recovery	.....
	F	29	Bloating gas; severe abdominal cramps; vomiting for 2 days	Abdominal tumor	Peritoneal holes sutured	Left para-duodenal	Recovery	.....
	M	26	Pain, colic for 2 wks.	Obstruction	Reduction	Transverse mesocolon	Recovery	Subsequent to posterior gastro-enterostomy
Sumner, 1929.....	M	66	Abdominal symptoms for years; symptoms obstruction	Intestinal obstruction	Reduction	Retro-peritoneal	Death	Autopsy, pneumonia
Thevenard, 1928.....	M	59	Operation for rectal neoplasm 3 mos. previously; sudden epigastric pain, fecal vomiting	Not given	Reduction	Foramen of Winslow	Death	Operation 5 days after onset
Traum, 1931.....	M	64	Acute pain in hypogastrium; vomiting	Acute appendicitis	Reduction	Ileo-appendicular	Recovery	.....
Turner and Scholefield, 1930	..	..	Acute abdominal pain, vomiting subsequent to operation for perforated ulcer	Intestinal obstruction	Two loops intestine punctured	Left para-duodenal	Death	.....
Venables, 1930.....	M	..	Chronic intestinal flatulence; diarrhea for 3 wks.; pain for 3 days	Partial obstruction	Reduction	Right para-duodenal	Recovery	Roentgenogram showed obstruction
Widgoff and Sturgeon, 1930	..	..	Severe generalized abdominal pain; vomiting for 5 hrs.	Acute appendicitis or obstruction	Reduction	Retrocolic	Recovery	.....
Watschugoff, 1931.....	M	24	Sudden pain, nausea	"Ileus"	Reduction	Fovea supracavicularis	Recovery	.....
	M	50	Pain for 4 days, vomiting	"Ileus"	Reduction	Fovea supracavicularis	Recovery	.....
	M	29	Sudden abdominal pain	Obstruction	Reduction	Fovea supracavicularis	Recovery	.....



Janes, who reported two cases of hernia through an opening of the left broad ligament, felt that these lesions can hardly be diagnosed before operation.

Donald reported a case of strangulated hernia in the retro-appendicular paracecal pouch. He was of the opinion that the pouch was caused by a lack of fusion between the mesocolon and the posterior parietal peritoneum in the terminal stage of embryonic rotation of the intestine. He said that he could find no previous description of this fossa and that neither Moynihan nor Short mentioned it.

TABLE 5.—*Comparison of Short's Figures with Those Reported by Other Authors*

Type of Hernia	Operation									
	Death						Died—No Operation			
	Recovery		Short		Others		Short		Others	
	Short	Others	Per Cent	Per Cent	Per Cent	Per Cent	Per Cent	Per Cent	Per Cent	Per Cent
Retroperitoneal.....	..	1	..	....	1	50.0	..	....	..	....
Paraduodenal										
Side not given.....	..	..	..	....	..	....	..	....	..	....
Left.....	27	4	16	37.2	1	33.3	..	....	..	....
Right.....	1	4	1	20.0	..	....	3	60.0	..	....
Duodenojejunal.....	..	4	..	....	..	....	..	....	..	....
Treitz.....	..	2	..	....	2	40.0	..	....	1	20.0
Paracecal										
Retrocolic.....	12	4	4	23.5	..	....	1	5.8	..	....
Ileo-appendicular....	2	3	1	20.0	1	25.0	2	40.0	..	....
Foramen of Winslow..	8	6	11	45.8	4	40.0	6	25.0	..	....
Intersigmoid.....	4	2	2	25.0	2	50.0	2	50.0	..	....
Transverse mesocolon.	6	7	..	....	..	....	..	....	1	12.0
Others.....	9	8	..	....	3	27.2	1	10.0	1	9.0
	69	45*	35	29.6	14†	21.3	15	12.7	3	42.3

Total number of cases: Short, 118 cases, 50 deaths; mortality 42.3 per cent.

Total number of cases: Others, 61 cases, 17 deaths; mortality 27.8 per cent.

\* Including two cases through the foramen of Winslow and one duodenojejunal hernia not quoted by Short.

† Including one case through the foramen of Winslow, one ileocecal and one through the omentum missed by Short.

The three cases reported by Watschugoff of intra-abdominal hernias of the fovea supravescicalis have been included here. They are definitely designated as of the internal type. Watson said that this type of hernia may be either external or internal. Watschugoff reported that in the past ten years in the Rasumowsky Clinic there were fifteen hundred operations for hernia, but only three of this type. He stated that sixteen similar cases have been reported by Reich.

Martzloff reported a case of prolapse of the intestine through a preformed opening in the great omentum. On inspection, two openings in the omentum in about the midline, a smaller and a larger one, were found. A loop of small intestine protruded through the larger defect and lay on the omentum to the right of the midline. His case differs from others in the literature in not having symptoms of intes-

tinal obstruction. There are, he said, sixteen such cases reported in the literature in which the opening in the omentum was preformed, and not the result of adhesions.

Four cases of intersigmoid hernia are reported here, in two of which the patient died following operation. Hamilton, who contributes one of the latter cases, said that Short had overlooked at least six cases. His own case, he stated, brings the total up to fifteen. The three additional cases collected here all occurred in males, which supports his statement that of the fifteen reported up to that time only two occurred in females. The youngest patient whose case has been reported was an infant  $3\frac{1}{2}$  days old (reported by Coley). The oldest patient was a man of 66 years.

Deaver (*a*), reporting a case of paraduodenal hernia, said that this condition is usually only discovered at autopsy. Of the twenty-nine cases which he quoted Nagel as reporting in 1923, operation was performed in twelve and ten were fatal. This would give a mortality of 83 per cent. Short reported five cases with one death following operation and three deaths without operation, a mortality of 80 per cent. Of the four cases of right duodenal hernia collected in this paper, recovery followed operation in all of them. Masson asserted that in no case has diagnosis been made before operation or autopsy. The case he reported resulted in recovery.

Turner and Scholefield, reporting a case they classed as duodenal retroperitoneal hernia, said that this is a very rare occurrence; that in Guy's clinical and postmortem reports from 1900 to 1925 there is only the one case.

Godard and Smith, writing of hernias of the retroperitoneal cavity, reported that Federschmidt has collected thirty-one cases of hernias through the transverse mesocolon and an additional fifty-two cases of internal hernia through the mesentery orifice. They consider that accidents to the mesentery are very rare, and that inflammation and neoplasm play a rôle no less important than traumatism. They mention the relatively high number of gastric or duodenal ulcers or carcinomas that exist with a hernia through the mesotransverse colon. Lombard, they said, reported carcinoma or ulcer eighteen times in twenty-eight cases. Cases are known in which such hernias are congenital. Pringle, in 1919, reporting eight cases, had one in a girl of 5 years and another in a boy of 5 months. The girl had a mesotransverse colon which was incompletely developed, and a large part of the jejunum had penetrated into the retrogastric pocket. Death resulted. The boy also died. Autopsy showed a very large space between the left and middle colic artery which was closed by a mesentery fringe. The hernias through the transverse mesocolon are considered by Godard

and Smith to be the most favorable of the internal hernias, though they frequently follow gastro-enterostomy.

Watson said that hernias through the transverse mesocolon are rare; that in sixteen hundred autopsies reported by Mitchell, in only three were there holes in the mesentery, and in no cases were hernias found. Heaney and Simpson reported that in twenty-one cases of this type, gastric or duodenal ulcer or carcinoma was present in fourteen, a finding in agreement with the belief of Godard and Smith. In fourteen cases in which sex was mentioned, thirteen of the patients were females. Heaney and Simpson consider a midline ptosis, which predisposes to ulcer and hour-glass stomach, an all important factor in the production of this type of hernia. It was definitely present in ten of twenty-one cases, and both of their cases showed it. Lefèvre also noted the frequent coexistence of gastric or duodenal ulcerous lesions and internal hernias, but said that cause and effect cannot be concluded from this. In his case he believed the orifice to be of a congenital nature.

Short reported seventeen cases of hernias through the transverse mesocolon, in six of which recovery followed operation. The fate in the other eleven is not given in his tabulation. In the eight cases reported since 1925, there was one death in a case in which operation was not performed.

Short collected twenty-four cases of hernia through the foramen of Winslow. In this paper are reported four additional cases which Short missed and seven cases which have been reported since his paper was written, bringing the number up to thirty-five. Short found a mortality of 70.8 per cent for this type of hernia, but the figures reported since then are lower, the mortality being 42.7 per cent. Deaver (*a*) said that this type of hernia presents a very difficult problem because of the danger incident to injuring the neck of the hernia, which has within its immediate vicinity the portal vein, the hepatic artery, the common bile duct, the inferior vena cava and the first portion of the duodenum. Jejunostomy is usually the only safe procedure. Dewis and Miller said that this type of hernia gives symptoms of epigastric discomfort, weight, swelling, fulness and pressure. There is absence of definite obstruction. With this conclusion, the cases reported here are in agreement. Gastric symptoms, often of long duration, predominate. In the case reported by Aigrot, there was a history of stomach trouble extending over twenty years.

Godard and Smith also spoke of the difficulties of reducing hernias through the foramen of Winslow. They report that often the difficulties are insurmountable.

Short reported seventeen cases of retrocolic hernia. To this list there have been added four more. Short's mortality is 29.4 per cent.

In the four cases reported in this paper recovery followed operation. The case of Vidgoff and Sturgeon is remarkable because the hernia involved the cecum, which formed part of the contents of the fossa. The authors said that this is the only case on record in which this has occurred.

As has been mentioned, hernia of Treitz is a term that Short does not use. In this paper six cases have been so classed by their authors. In addition, there were two cases that Garber quoted and that are listed in tables 1 and 2. In two of the six cases, operation was not performed, and the hernia was discovered at autopsy. In the remaining four death occurred in two following operation. In one of these cases the hernia was only discovered at autopsy. Short said that ninety cases are known, the patients ranging in age from 2 months to 80 years; that the male sex predominates, and generally it is believed there is an embryonal disposition and that the hernia develops as the result of a mechanical factor on a disposition already present. Garber listed the usual symptoms of this type of hernia as follows: (1) dyspeptic symptoms; (2) sensation of tumor in the abdomen, localized and periodically changing in size; (3) periodic swelling of the abdomen, and (4) tympanic sound over the abdomen. Christophe expressed the belief that duodenojejunostomy is the operation of choice in this type of hernia when reduction is impossible.

Spitzmuller reported a case of double hernia (colonic rectal ileus and internal rectovaginal) which, because of its complex nature, has not been included in the tables. The left scrotal hernia was evident, but operation revealed the double hernia. Reduction of the hernia resulted in recovery.

#### MORTALITY FIGURES

In looking over table 4 it will be seen that of the sixty cases operation was performed in fifty-two; eleven of the patients died and forty-one recovered. Of the nineteen deaths, five were due to causes other than hernia, and the hernia was discovered only at autopsy. Thus in Lieber's case death was due to tuberculosis; in Stangl's case death was due to accident; and in the three cases of Siegmund death was due, respectively, to grip, angioma and appendicitis. Three of the remaining fourteen patients who died were seen in the terminal stage when operation was no longer possible. These were the cases of Odermatt, Debray and Muller. Of the eleven cases in which operation was done and in which death ensued, delay before operation or the fact that the hernia was undiagnosed even at operation played a major part in the cause of death. McCarthy's patient was already in shock when seen, and it was not until eighteen hours after the onset of the condition that the operation was done. Delay undoubtedly contributed to death

in Thevenard's case. The first physician to see the man ordered a purgative, and the patient was not brought in for operation until five days after the onset of the symptoms. In James' second case an exploratory operation was done in spite of a bad cardiac condition, and death followed from myocardial failure. It was only at autopsy that the cause of the abdominal symptoms was found to be hernia.

Christophe reported a case of hernia of Treitz which illustrates perfectly the difficulty in diagnosing this condition, as well as the dangers attendant on a late diagnosis. His patient, who had suffered from dyspeptic troubles for five years, and for two years with alternative diarrhea and constipation, suddenly, six weeks before, had abdominal pain and noted a tumor. A preoperative diagnosis could not be made, and roentgenograms revealed no obstruction. An exploratory operation was performed, and what was supposed to be a retroperitoneal ganglionic tumor was found. The wound was closed. There was temporary amelioration following the operation, then the condition became worse, the roentgenogram showed a dilated duodenum, and a resistant mass was felt in the left hypochondriac region. Duodeno-jejunosomy was refused until the condition was very bad. The operation was performed, and a hernia was found and reduced. Death followed from a laryngitis not severe in itself, but fatal because of the extreme cachetic condition.

In Christophe's second case, in which death followed a celiotomy, symptoms of intestinal obstruction had been present for a week. Dewis and Miller reported a case in which, at operation, they found and drained what they thought to be a tumor. At autopsy the true condition, a hernia, was disclosed. Donald's patient with symptoms of acute obstruction beginning four days before the operation died two hours after being operated on.

In a few instances death was not directly due to the hernial condition. Thus Sumner's patient died of pneumonia, and Hamilton's patient of aneurysm on the nineteenth postoperative day.

These figures show without doubt that delay in operation is far too often the cause of fatality.

Diagnosis is exceedingly difficult before operation and, as has been mentioned, in more than one case the true condition is not discovered at operation. In many cases the immediate symptoms are those of intestinal obstruction, as would be expected, since incarceration or strangulation of the hernia is common. In addition to the preoperative diagnosis of obstruction, the diagnoses of perforated ulcer and of appendicitis are both common. When palpation reveals a mass, the diagnosis may be cyst or malignancy. The only instances in which a hernia was suspected before operation were the cases of Erdély, Jackson, and Coley and Hoguet. In Jackson's case the diagnosis was made

by roentgenogram. In the case of Coley and Hoguet the mass was palpated, but the physicians called in consultation were unable to confirm this finding before operation. Gastric symptoms are frequently of long duration, and in many instances there are recurring attacks of pain and vomiting. These are frequent enough to be considered characteristic.

The mortality in the reports in the literature since Short's article is much less than that given by Short. These are given in detail in table 5, and compared there with those of Short. In the sixty-one cases here reported with hernia in which operation was performed, or in which death occurred without operation as a direct result of the hernia, there were seventeen deaths, or 27.8 per cent. This compares favorably with Short's figure of 42.3 per cent. In the cases in which operation was performed Short reported a mortality of 29.6 per cent, while the mortality in the cases reported here in which operation was performed is only 21.3 per cent.

#### SEX AND AGE

Internal hernia is more common in males than in females. From the cases here reported the ratio is better than 2:1, there being thirty-six cases in males and only fifteen in females. The youngest patient, a 10 year old boy, had a hernia through the mesentery (case reported by Judd). The oldest patient was a man of 74 who died of appendicitis without operation (case reported by Siegmund). The average age is 38, but there are only six cases in the forty-eight in which the age is stated in which the patient is less than 20. There are fifteen patients, or almost one-third, who are 50 or over.

#### TYPE OF OPERATION

The difficulties of diagnosis have already been noted. The symptoms, while not sufficiently differentiated from other gastric and abdominal complaints, are usually sufficiently severe, especially when strangulation is present, to warrant immediate operation. The type of operation depends largely on the condition of the bowel. In many instances simple traction will be sufficient to reduce the hernia, and often the release of the obstruction will be sufficient to restore normal blood flow and color, making more radical procedure unnecessary. When adhesions are present they must, of course, be cut away. Occasionally the pouch incarcerating the bowel needs to be divided. When necessary, jejunostomy, end-to-end anastomosis and other radical procedures must be performed. A glance at table 4 will show that where such procedures have been necessary the mortality has been greatly increased.

## CAUSES

Some mention has been made already of the various opinions as to the cause of internal hernia. Little can be added. Trauma, congenital defects, previous operations, ulcers and malignancy all have played their part. In most instances the direct cause of the condition cannot be discovered, and speculation is idle.

## SUMMARY

1. A review of the literature of internal hernia since Short's article has been made and the cases collected.
2. A systematic classification of internal hernia is given.
3. Tables showing the mortality, frequency of the various types and a list of the collected cases are given.
4. Three new cases are reported.

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# RADIOSENSITIVENESS OF CELLS AND TISSUES, AND SOME MEDICAL IMPLICATIONS

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Casual reading of contemporary medical records bearing on the action of roentgen rays and radium often gives the impression that little is known of such action in spite of the fact that substantial or conclusive experimental data are available to indicate or to establish clearly the nature of it. In some cases, indeed, the experimental indications are absolute. In other cases, the experimental evidence may be inadequate, but the clinical data may be sufficient to suggest the probable effect of irradiation. It is true that many problems relating to radiotherapy are still the subject of controversy, and that the large number of experiments that have been made have yielded only partial answers to many questions. Nevertheless, the facts already brought to light are sufficiently numerous to provide an imposing, although admittedly incomplete, scientific background. Unfortunately, the evidence furnished by experiments on animals and clinical observation has never been analyzed and correlated, and much of it has been lying on library shelves, buried in medical or other journals that are seldom read. Even among medical radiologists knowledge of the experimental background is not widely diffused.

The law based on the extensive investigations of Bergonié and Tribondeau (1904-1907), according to which young or immature cells are more radiosensitive than old or adult cells, has been generally recognized and has long been regarded as the essential foundation of radiotherapy. Numerous experiments have shown that direct irradiation of the pregnant uterus or of the young soon after birth causes retardation of growth of the skeleton and of various organs, including the brain. The degree of such effect varies with the dose, the age of the animal and the natural life cycle of the species. The cells and tissues of a given species rapidly become less sensitive as the animal emerges from the early phase of its existence, during which growth is a prominent feature. Indubitable as is the relation of the age of cells to radiosensitiveness, analysis of the experiments made to test the susceptibility of different organs and tissues brings out the even more important fact that each

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Read in abridged form before the summer meeting of the American Association for the Advancement of Science, Pasadena, Calif., June 15, 1931.

From the Section on Therapeutic Radiology, the Mayo Clinic.

variety of cell in the body has a specific sensitiveness, or rather a specific range of sensitiveness, to irradiation. This is not intended to imply that all cells of one kind, such as lymphocytes or squamous epithelial cells, react in precisely the same way to a given dose of rays. A certain measure of variation in reaction must occur, because different cells of the same kind are struck by the rays while in different stages of metabolism. Other still unknown factors also may play a part. However, if allowance is made for such variation, and if reaction time is taken as a criterion, the specific sensitiveness of each kind of cell looms up as the dominant single fact of radiology and deserves to be recognized as a law. And yet, if one may judge by present day writings, the existence of such a law and of its medical and biological implications is not at all realized. For years much has been made of the dogma that pathologic cells are more radiosensitive than normal cells of the same kind, but, as Lazarus-Barlow and others have shown, the foundation on which this dogma rests is tenuous and insecure. The physiologic condition of cells undoubtedly has some influence on their sensitiveness, but, as I shall bring out presently, this influence is small as compared with the specific natural susceptibility of each variety of cell. Although the factors responsible for such specificity have not yet been determined, the sensitiveness peculiar to each kind of cell appears to be related chiefly to the natural life cycle. Thus the lymphocytes, the metabolic cycle of which among human cells is the shortest, are also the most radiosensitive, and the nerve cells, the life cycle of which is the longest, are also the most resistant to irradiation. But to this question as to many others the final answer has not yet been given.

When a living tissue or organ is exposed to roentgen rays or radium, a more or less important proportion of the cells may subsequently exhibit temporary inhibition of metabolic activity or complete and permanent disintegration, or may not show any deleterious effect. Moreover, if the time intervening between irradiation and perceptible reaction is taken as a criterion, it will be found that certain species of cells react more rapidly than others to a given dose, or that the degree of reaction to the same dose is greater for some kinds of cells than for others. According to present knowledge, cells may be classified, according to their radiosensitiveness, in the following order:

Lymphoid cells (lymphocytes)

Polymorphonuclear and eosinophilic leukocytes

Epithelial cells: (1) basal epithelium of certain secretory glands, especially of the salivary glands; (2) basal epithelium (spermatogonial cells) of the testis and follicular epithelium of the ovary; (3) basal epithelium of the skin, mucous membranes and certain organs, such as the stomach and small intestine; (4) alveolar epithelium of the lungs and epithelium of the bile ducts (liver), and (5) epithelium of tubules of the kidneys

Endothelial cells of blood vessels, pleura and peritoneum

Connective tissue cells  
Muscle cells  
Bone cells  
Nerve cells

Although the difference in susceptibility between the most sensitive and the least sensitive varieties of cells is considerable, none of the cells are wholly invulnerable to irradiation; all cells, whatever their variety, may be destroyed or injured if exposed to a sufficiently large dose of rays, especially if doses within the therapeutic range are disregarded.

#### RADIOSENSITIVENESS OF DIFFERENT SPECIES OF CELLS

*Lymphoid Cells.*—Of the different kinds of cells that make up the tissues and organs of the body, the most susceptible by far are the lymphocytes. This important fact was brought to light by the early and extensive experiments of Heineke (1903, 1904, 1905) and has since been fully confirmed by the subsequent investigations of Warthin (1906), Krause and Ziegler (1906-1907), Fromme (1917), Hartmann (1920), Jolly (1924), Tsuzuki (1926), Piepenborn (1929) and others. When, using different species of animals, Heineke exposed the entire body to roentgen rays, he found that most of the tissues and organs remained unaffected, but that the spleen, lymph nodes, intestinal lymph follicles, circulating blood, bone marrow and all agglomerations of lymphoid cells showed a more or less pronounced destruction of lymphocytes. The degree of destruction was proportional to the dose of rays and varied with the interval between irradiation and death. In the spleen, lymph nodes and other lymphoid structures, the destruction of lymphocytes started around the germinal center and gradually extended toward the periphery of the follicle. As the number of intact lymphocytes diminished, the stroma became prominent, and often this feature was so pronounced that the follicles could be recognized only by the blood vessels and the concentric arrangement of the stroma. Heineke observed such destruction of lymphocytes as early as two hours after irradiation. The extent and duration of the destructive phase depended on the intensity of irradiation; the destruction continued for several days and was accompanied by a progressive reduction in volume, or atrophy, of the affected structures.

As described by Heineke, such destruction is characterized by disorganization and fragmentation of the nuclear chromatin and by scattering of the fragments of chromatin between the remaining intact cells and in the reticular spaces, where the fragments gather into clumps or balls. Then the clumps or balls of degenerate chromatin are gradually taken up by some of the reticular cells, which assume a phagocytic property and swell as the amount of ingested chromatin debris increases. The disposal of chromatin material from the destroyed

cells continues until all such material has undergone phagocytosis. The nuclear débris ingested by the phagocytes apparently undergoes intracellular digestion, because the number and the size of the ingested fragments diminish steadily. Some hours later the phagocytic reticular cells themselves begin to disappear. After a single massive irradiation or repeated moderate doses, all the lymphocytes may be destroyed, but after a single small or moderate dose a certain proportion of the cells appear to resist the action of the rays. From one to three weeks after exposure, if the irradiation has not been sufficiently intense to destroy all the lymphocytes, more or less regeneration of the lymphoid tissue may be observed, and complete cellular restoration may occur. Two or three days after exposure to roentgen rays, degenerative alteration of other cells, notably the polymorphonuclear and eosinophilic leukocytes, also becomes perceptible, and many of these cells disappear from the splenic pulp and bone marrow.

Warthin's description of the effect of roentgen rays on the lymphoid structures corroborates the observations of Heineke in every particular, except that, by examining the tissues soon after irradiation, Warthin found unmistakable evidence of the disintegration of lymphocytes within fifteen minutes after exposure of the animals to the rays, and the cellular degeneration continued for several days. Similar effects were obtained with radium by London (1903), Heineke (1904), London (1905), Thies (1905) and Lazarus-Barlow (1922). Rudberg (1907), Aubertin and Bordet (1909), Arella (1910), Regaud and Crémieu (1912) and others have likewise shown that roentgen rays and radium exert precisely the same influence on the small round cells of the thymus gland, and their work strongly supports Hammar's conclusion that the small cells of the thymus gland are indeed lymphocytes. Others, notably Senn (1903), Heineke (1903, 1905), Guilloz and Spillmann (1904), Aubertin and Beaujard (1904, 1905, 1908), Brown (1904), Bryant and Crane (1904), Capps and Smith (1904), Helber and Linser (1905), Benjamin, von Reuss, Sluka and Schwarz (1906), Aubertin and Delamarre (1908), Taylor, Witherbee and Murphy (1919), Russ (1919, 1921) and Leitch (1921), have proved conclusively that the lymphocytes in the circulating blood are equally sensitive to irradiation and also are destroyed in large numbers by exposure to roentgen rays or radium.

*Epithelium of the Salivary Glands.*—Next to the lymphocytes in point of radiosensitiveness are the basal epithelial cells of the salivary glands. Actually these cells are more sensitive to irradiation than the polymorphonuclear and eosinophilic leukocytes. This is evidenced by the fact that, whereas microscopically perceptible changes in the two latter varieties of cells can seldom be found within the first six hours after exposure to the rays, clinical signs of salivary reaction can

usually be observed in from three to six hours after irradiation. These signs consist in swelling, redness and tenderness in the region of the irradiated glands and, when bilateral, may simulate the salivary phase of mumps. If all the glands on both sides have been exposed to the rays, the foregoing clinical signs may be rapidly followed by decrease in salivary secretion, often leading to dryness of the mouth lasting from a few days to two or more weeks. This reaction of the salivary glands is characterized by mucoid degeneration of the basal epithelium. The cells swell, the excretory ducts become occluded, and the secretion accumulates within the glands—hence swelling and tenderness of the glands and dryness of the mouth. Following a single irradiation, salivary reaction is always transient; after a time, usually from twenty-four to seventy-two hours, the acute phase of the reaction subsides, and the clinical signs gradually abate. Following repeated irradiation, however, the secretory function of the glands may cease, and dryness of the mouth may persist for a long time. Such effects occur only when the glands on both sides have been exposed to the direct action of the rays. Salivary reaction does not occur when other parts of the body are irradiated, and exposure of the glands on one side causes a reaction on that side only. When the reaction is unilateral, dryness of the mouth is seldom noticed, undoubtedly because the glands on the opposite side furnish a sufficient quantity of saliva to lubricate the oral mucosa. The experiments of Lazarus-Barlow (1922) and of Mottram (1923) indicate that epithelial cells that produce mucus are much more sensitive to irradiation than other epithelial cells. The first effect is mucoid degeneration with excessive and abnormal production of mucus, followed by arrest of the formation of mucus. This has been shown to occur in the intestine, and the behavior of the salivary glands under irradiation makes it seem likely that the mucus-producing cells in the epithelial lining of these glands are similarly affected by the rays.

*Epithelium of the Testis and Ovary.*—The testis is not so sensitive as some of the leukocytes or as the salivary glands, but with the exception of these, is the most sensitive structure in the body. This susceptibility has been established by numerous experiments on animals, as well as by the cessation of seminal function in radiologists and other persons exposed to roentgen rays over a long period of time. The radiosensitiveness of the organ is due to the susceptibility of the spermatogonial cells, which are affected deleteriously even by a moderate dose of roentgen rays. The cells of Sertoli are relatively resistant to irradiation, and this fact tends to support the view that they supply nourishment to the basal layer of seminal cells, the spermatogonia. The spermatocytes of the first and second order, as well as the spermatids and mature spermatozoa, are distinctly less sensitive than the spermatogonia and are affected only by larger doses. Even so, much of the

cellular degeneration is probably secondary to the direct action of the rays on the basal cells. Microscopic examination of the seminal tubules several days after irradiation may disclose vacuolization and degeneration of some or all of the spermatogonia, depending on the dose of roentgen rays to which the organ has been exposed. After a sufficiently large dose, degeneration of the spermatogonia proceeds to complete disintegration. This is accompanied by failure of the cells to evolve into spermatocytes and mature spermatozoa, and the final result is permanent azoospermia. After a dose insufficient to cause permanent azoospermia, a certain proportion of the spermatogonia may be able to survive and may serve as a nucleus for histologic regeneration and functional restoration. Large doses repeated at comparatively short intervals are almost certain to induce permanent sterilization. The interstitial tissue, on the other hand, is much more resistant and is not perceptibly influenced by ordinary therapeutic irradiation. Needless to say, however, that even the interstitial tissue could be irreparably injured by excessive irradiation beyond the therapeutic range.

The radiosensitiveness of the ovary is essentially the same as that of the testis, and the cells to which the specific susceptibility of the gland is due are the ova and the epithelium of the follicles. The sensitiveness of different follicles varies according to the stage of development. Depending on the dose of rays to which the ovary has been exposed or on the number of times a given dose has been repeated, the effect of irradiation may be disintegration and disappearance of a certain proportion of the follicles or complete and permanent destruction of every follicular structure. A certain proportion of the primordial follicles may escape if the dose has been small. Moreover, the steps in the reaction of the follicles are analogous to those of spontaneous physiologic atresia. Follicular reaction appears from three to six hours after exposure and is particularly marked in the mature follicles. In the primordial follicles, the rays act on the ovum sooner than on the follicular epithelium, and this action is featured by pyknosis of the germinal vesicles, condensation of the protoplasm and finally by chromatolysis and fragmentation of the cell. The cellular fragments then undergo phagocytosis by the follicular epithelial cells, which themselves degenerate as soon as phagocytic disposal of the fragmented ova is complete. These different steps require three or four days, but since all the follicles do not begin to react at the same time, a week or more may elapse before all the affected follicles have disappeared. The same cycle of changes occurs in the more mature follicles with several layers of epithelium, but in these the follicular epithelium is more sensitive, and its cells undergo rapid autolysis. Moreover, the connective tissue cells of the theca interna degenerate as rapidly as the epithelial cells. In the still more mature follicles, in which the ovum

is large and separated from the follicular epithelium by a membrana pellucida, the epithelial cells first penetrate this membrane by diapedesis, dispose of the degenerated ova by phagocytosis, and in turn degenerate and disappear. Migration of the epithelial cells begins about the third day, and the degenerative process continues for two or three weeks. All such follicles may be destroyed by irradiation, but on account of the large size of the ova the autolytic process may require considerable time. In fully developed follicles, the epithelial cells are still more sensitive, most of the parietal epithelium of the follicular cavity being destroyed by irradiation, whereas the epithelial cells that surround the ovum are slightly less sensitive. Sometimes irradiation may be followed by an accelerated maturation of the ovum followed by degeneration. Thus the radiosensitiveness of ovarian follicles increases in proportion to their development. The interstitial cells of the ovary do not appear to be influenced directly by the rays, but slowly disappear, probably because the destruction and disappearance of the follicles prevent the interstitial cells from being renewed.

*Epithelium of the Skin, Mucous Membranes and Gastro-Intestinal Tract.*—The skin can tolerate with impunity a considerable single dose of roentgen rays, but when the limit of tolerance is exceeded, it may undergo a series of reactive changes. The first clinical manifestation of excessive irradiation is a readiness of the hair in the exposed territory to fall out. After a still larger dose not only does epilation occur, but varying degrees of reactive inflammation of the skin may take place. Dermatitis may appear as a slight erythema lasting a few days and followed by pigmentation corresponding to the exposed area; as a more pronounced, bright red erythema with a sensation of heat, followed by the formation of vesicles and later by itching, exfoliation of the epidermis and deep pigmentation; or, in extreme cases, as an intense, painful erythema, with or without fever, and followed by more or less extensive ulceration of the entire thickness of the skin. Mild radiodermatitis may not leave any permanent marks beyond slight atrophy of the irradiated area of skin, provided the inflammatory reaction results from a single exposure. When such reaction appears after the same area of skin has been exposed several times, it is likely to be followed, from one to three years later, by telangiectasis. The sudoriferous and sebaceous glands of the irradiated skin also undergo degenerative changes. Radiodermatitis accompanied by the formation of vesicles is followed by more extensive desquamation or by the actual formation of small rounded, or large irregular cutaneous scars. When severe radiodermatitis is followed by ulceration, the ulcers are slow to heal. This is due partly to the peculiar character of injury produced by irradiation and partly to secondary infection, which so commonly complicates the ulceration. Severe radiodermatitis generally

results from inexperience, from miscalculation of some of the factors in dosage, or from accidental omission of a filter with a dose based on the use of filtered rays.

The rays act first on the epithelium of the hair follicles, and this explains the loosening or falling of the hair. Such elective sensitiveness of the hair follicles is made use of in the treatment of diseases of the skin such as ringworm, in which the dose of roentgen rays is adjusted so as to cause temporary epilation. The success of the treatment rests on the ability of the radiologist to regulate the dose within narrow limits; any uncertainty in this respect may result in permanent alopecia or worse. When the dose has been sufficient to cause distinct erythema, the microscopic changes include irritative disturbance of the basal layer of cells accompanied by hyperemia and edema, and later by degeneration and desquamation of the epidermis. After larger single doses, these alterations may be marked and may extend to all the layers of the skin. The rays also act on the endothelium of the blood vessels, causing these cells and sometimes the media to swell, undergo hyperplasia, and later proliferation of connective tissue, which may lead to reduction in caliber or to actual obliteration of the vessels. This serves to explain in some measure the slow healing of radiodermatitic ulcers, an explanation further substantiated by the fact that a dose several times greater may be given to a small area of skin (1.5 to 2 cm. or less) without causing ulceration.

Besides the foregoing acute effects there exist two varieties of late effects. One variety is featured by late necrosis of the skin in a region subjected, several months or even several years before, to repeated irradiation to the point of inducing early lesions such as have been described. The necrosis commonly follows slight trauma, but may occur without any apparent, immediate cause. It begins with redness, pain, swelling and a sensation of heat, and a short time later progressive ulceration similar to that typifying early radiodermatitis of the third degree develops. Probably the chief determining cause of late ulceration is infection of the connective tissue, the natural resistance of which has been impaired by obliterative changes in the blood vessels and other chronic changes in the connective tissue itself. A second variety of late radiodermatitis is experienced by physicians or others who may have been exposed to roentgen rays at frequent intervals for a long time. Usually it affects the hands and sometimes the face. The lesions appear only after years of daily exposure and consist in thickening of the skin, with redness and sensitiveness, often also in dryness and brittleness of the nails. The skin becomes harsh and tends to crack easily, and areas of keratosis develop, which later may undergo epitheliomatous transformation. Many pioneers in roentgenology have



had the misfortune to pay for their ignorance of the danger or for their carelessness with the loss of fingers, hands or entire extremities, and a number have lost their lives.

The sensitiveness of the epithelium of mucous membranes is much the same as that of the skin. Excessive single irradiation causes first anesthesia, then dryness, redness from hyperemia, and edema. Depending on the dose, these clinical manifestations may abate and disappear or may be followed by ulceration. Repeated excessive exposures cause hyperplastic thickening of the epithelium, and this may be followed by necrosis. The radiosensitiveness of specialized mucous membranes, such as the mucosa of the stomach and intestine, varies with each structure. Irradiation of the stomach causes temporary reduction in the secretion of gastric juice, and this affects the production of hydrochloric acid and pepsin. If the stomach is exposed repeatedly at relatively short intervals, the gastric acidity and pepsin fall lower and lower, and this may continue for weeks or months. If the exposures were repeated indefinitely, the secretory activity of the gastric mucosa might be completely and permanently arrested. The susceptibility of the intestine varies in its different parts. The mucosa of the colon is relatively insensitive to the action of the rays; at least, it is much less sensitive than that of the small intestine. The most sensitive portion of the mucosa of the digestive tract is that of the duodenum and jejunum, which may be irritated by doses insufficient to disturb the overlying skin. When the upper half of the abdomen is exposed to a therapeutic dose of roentgen rays, anorexia, nausea and vomiting often follow within a few hours, and diarrhea may appear several days later. Exposure to excessive doses, such as have been employed in many experiments on animals, causes mucoid degeneration of the intestinal epithelium, hyperemia and edema of the mucosa and submucosa, and such changes may be followed by desquamation of the epithelium. According to the severity of the reaction, the epithelium may regenerate, or the breach in the mucosa may be repaired by connective tissue.

*Epithelium of the Lungs and Liver.*—The lungs are comparatively resistant to the action of roentgen rays, but if the overlying skin is exposed to a grossly excessive dose, especially if such a dose is repeated several times or if the thoracic wall is thin, reactive pneumonitis is likely to follow. This may subside spontaneously without any after effects, or may be followed by fibrous repair and by slight or marked impairment of respiratory function.

On the whole, the liver is still less radiosensitive than the lungs. Most of the pathologic changes in the liver that have been found after experimental irradiation of animals have not been a direct effect of the rays, but an indirect effect of cellular changes in other more sensitive structures. The epithelium of the biliary ducts appears to be slightly

more sensitive than the hepatic cells themselves, but it is not clear whether such alterations as have been observed resulted from a direct action of the rays, or whether they also were secondary to the circulation of toxic products of cellular degeneration in remote organs.

*Epithelium of the Kidneys.*—The kidneys can hardly be regarded as radiosensitive organs, as far as therapeutic doses of roentgen rays are concerned. Yet excessive irradiation may cause slight, moderate or severe reactive nephritis. The cells first affected are the epithelial cells of the convoluted tubules. Nephritis in radiotherapy of human beings should immediately suggest either gross overdosage or excessive elimination of toxic products of cellular degeneration in other, more sensitive structures or tissues. Certain experiments on animals have shown that, if therapeutic doses are disregarded, the organ may undergo reactive inflammation leading to chronic nephritis, with increase in blood pressure and the usual reverberations associated therewith. Such an effect merely goes to show that the kidney, like all other organs or tissues, is not wholly insensitive to irradiation but may be injured more or less severely and permanently if its tolerance is exceeded. But it must not be inferred that ordinary therapeutic irradiation of the kidneys is dangerous.

*Endothelium.*—The radiosensitiveness of the endothelium of blood vessels, pleura and peritoneum is approximately the same as that of the skin. In other words, a dose of roentgen rays insufficient to irritate the skin is not likely to have an appreciable effect on the endothelial cells. When the tolerance of the skin is exceeded, however, the endothelium is likely to suffer temporary or permanent injury. The effect of a grossly excessive dose on the blood vessels is swelling of the endothelial cells, some or all of which in the irradiated area may degenerate and desquamate into the lumen of the vessel. The media also may swell more or less. As the acute phase subsides, the destroyed cells are replaced by hyperplasia of adjacent cells that may have suffered less, and the intima or the entire wall of the vessel may thicken by hyperplasia of connective tissue. The result is a slow narrowing of the lumen, which may or may not proceed to complete obliteration. Similar changes may occur in the pleura and peritoneum. Naturally, the effect of excessive irradiation may not be confined to these structures but may extend to the underlying parenchyma of the lung or to the wall of the intestine or other tissues underlying the peritoneal endothelium. Endothelial degeneration is usually accompanied by hyperemia and serous exudation, and may subside completely or terminate by chronic adhesive pleuritis or peritonitis. If the dose of roentgen rays has been sufficiently intense, the injury to the underlying tissues may outweigh the effect on the endothelium and may have

serious consequences. It is important, therefore, to keep the dose within safe therapeutic limits.

*Connective Tissue Cells.*—Young, freshly formed connective tissue cells are more sensitive, and mature connective tissue cells are less sensitive to irradiation than the epithelium of the skin. Young connective tissue, in a healing traumatic or surgical wound for example, is peculiarly sensitive to roentgen rays and, even after moderate therapeutic exposure, becomes more porous and more brittle. Moreover, moderate therapeutic irradiation of such connective tissue diminishes its formation or tends to hasten the granulation process. This effect appears to be due to the action of the rays on leukocytes infiltrating the area, and the connective tissue changes, therefore, are partly secondary or indirect; but a direct effect on the connective tissue cells also occurs. This is evidenced by the influence of roentgen rays on keloids, for which radiotherapy is the most effective treatment. Mature connective tissue cells, on the other hand, are distinctly more resistant than the epithelium of the skin, but if a dose beyond the tolerance of the skin is given, the connective tissue cells in the exposed territory may also be affected more or less. Some may be destroyed and give rise to fresh connective tissue. This probably has led to the assumption that the formation of such tissue may be stimulated by irradiation. The stimulation is never a direct result of irradiation, but is an indirect effect and always implies an antecedent destruction of cells of the same or of some other variety.

*Muscle Cells.*—The cells that typify voluntary or involuntary muscles also may be injured or destroyed by exposure to roentgen rays beyond therapeutic limits, but this involves still greater injury or destruction of the overlying tissues or implies convergence on the muscle of several beams of rays through as many separate fields. Muscle cells are comparatively resistant to the action of the rays and can readily tolerate ordinary therapeutic doses. Pathologic changes, such as the fatty degeneration sometimes observed in muscle cells after irradiation, usually result from the circulation of toxic products of cellular degeneration in other more sensitive tissues or structures.

*Bone Cells.*—Bone has long been thought impervious to the influence of roentgen rays and radium. It possesses a relatively high degree of resistance, it is true, but sufficiently intense or repeated irradiation may cause the bone cells to degenerate. The degree of such degeneration varies with the dose and with the age of the irradiated animal or person. In early life, the growth of bone can readily be retarded or permanently stopped by therapeutic irradiation, especially if the exposures are repeated. Adult bone, however, is able to tolerate rather large doses without apparent effect, but doses beyond the therapeutic

range may cause bone cells to degenerate and the bone to become devitalized. In the absence of infection, devitalized bone is slowly replaced by ingrowing new bone, especially if the affected bone is used for weight bearing. When, on the contrary, mechanical function is prevented by fracture or otherwise, the devitalized bone separates as a sequestrum, which is slowly absorbed. Secondary infection of bone devitalized by irradiation leads to the formation of a sequestrum regardless of function.

*Nerve Cells.*—As far as experimental evidence shows, the neurons of the central nervous system are the least radiosensitive of all cells. The brain and spinal cord can tolerate maximal therapeutic doses and even more with apparent impunity. But this does not mean that the specific cells of the nervous system are entirely invulnerable. Nevertheless, in many experiments on animals, in which doses several times greater than those used in the treatment of human beings were administered to the brain or spinal cord, the nerve cells did not show any perceptible evidence of a direct action of the rays. Such cellular changes as have been found after irradiation appeared to be secondary to the action of the rays on the cerebral vessels, the endothelial lining of which is more sensitive than the nerve cells themselves.

*Stimulating Effect of Irradiation.*—For years the legend that roentgen rays or radium, under certain conditions of dosage, may increase the growth and metabolism of cells has gained wide circulation. This notion has arisen from the attempt to apply to these agents the so-called Arndt-Schulz law, according to which small doses stimulate and large doses depress cellular metabolism. Based on pharmacologic grounds, this doctrine has not been generally accepted, even by pharmacologists. The attempt to apply it to the action of roentgen rays is unwarranted, because the experimental evidence on which it is based is extremely meager and apparently invalid. That a measure of acceleration in cellular metabolism may occur under certain conditions has been shown repeatedly both in animals and plants, but such unusual acceleration is a transient phase of reaction and is invariably followed by more or less pronounced cellular degeneration and inhibition of function. Another factor in the propagation of this notion of a stimulating action of the rays has been the regression of pathologic lesions after exposure to small doses of roentgen rays. Such regression is best explained by the exceptional radiosensitiveness of certain varieties of cells. As the result of primary degeneration of certain cells, a secondary or indirect stimulation may sometimes be observed. Such is the increase in connective tissue cells in certain tissues and organs after repeated irradiation; the connective tissue is laid down to replace other cells which the rays have caused to undergo degeneration. Any primary or direct

acceleration of cellular metabolism must be regarded as an effort of the cell to counteract or compensate for the noxious influence of the rays; in other words, it is purely a defense reaction. Continued acceleration of metabolism cannot be induced by roentgen rays or radium, which always cause degenerative changes or have no effect whatever. Irradiation of certain tissues, such as the skin, repeated over a long period of time may cause hyperplasia of the epithelium, and this in turn may lead to malignant transformation. This is not stimulation in the sense here employed, but alteration of a normal function to an aberrant one due to chronic irritation.

*Comparative Influence of Rays of Different Wavelength.*—Roentgen rays and radium have the same general effect on living tissue. Such variations as may be observed can be accounted for by difference in the methods of irradiation with each agent. Unfiltered radium buried in the substance of a tissue produces an intense destruction of cells immediately adjacent to the radioactive unit. The degree and extent of destruction can be modified at will by filtration. The conditions under which roentgen rays are generated precludes anything but external irradiation. If the effect of external irradiation with radium is compared with that of similar irradiation with roentgen rays, any variation attributable to difference in wavelength will be small; the greater part of the difference must be charged to variation in the total quantitative dose of each kind of energy. Quality of radiation plays a definite part in the effect, but this part is much smaller than the part played by quantity of radiation. To illustrate this further I need only draw attention to the difference of action between unfiltered roentgen rays of relatively long wavelength and rays of short wavelength generated at voltages of 80 and 200 peak kilovolts, respectively. A dose of the former beyond the tolerance of the skin to an area more than 1 inch (2.5 cm.) in diameter is likely to result in ulceration, whereas a corresponding dose of rays of short wavelength seldom causes ulceration, but usually induces a dense brawny induration of the skin and subcutaneous tissues and adhesion of the underlying muscles.

#### OUTSTANDING MEDICAL IMPLICATIONS

To attempt to deal adequately with this phase of my subject would be to risk overtaxing the reader's patience. I shall confine myself, therefore, to a brief outline of the more important medical relationships.

*Radiotherapy for Inflammatory Conditions.*—Knowledge of the specific sensitiveness of different species of cells to roentgen rays or radium is of fundamental importance in the treatment of inflammatory lesions as well as in the diagnosis and treatment of certain neoplastic

processes. It has long been known that many acute or chronic, suppurative or nonsuppurative inflammations are favorably influenced by roentgen rays or radium. In some of these conditions, indeed, irradiation has been found to be the therapeutic method of choice. Among the acute inflammations amenable to such treatment may be mentioned furuncle, carbuncle, lymphadenitis, pneumonia in certain stages, parotitis and erysipelas. The more acute the process the more quickly it responds to irradiation and the smaller the dose required. Exposure of such lesions at an early stage (phase of leukocytic infiltration) usually causes them to undergo rapid resolution. Irradiation at a slightly later stage (phase of beginning suppuration) hastens the suppurative process. In both cases, but especially in the former, the course of the inflammation is shortened, and pain is quickly allayed. Usually, a single exposure to the rays is sufficient. Tuberculous lymphadenitis, tuberculosis of the cornea and iris, trachoma, actinomycosis and many diseases of the skin may be cited as examples of chronic inflammation amenable to radiotherapy. In such conditions, however, treatment must be repeated at intervals for some time. The rate and mode of reaction of inflammatory lesions indicate that the rays act chiefly by destroying the infiltrating lymphocytes, the exceptional sensitiveness of which has already been pointed out. The rate of reaction of acute inflammations corresponds so closely to the rate at which normal lymphocytes are known to be destroyed by the rays that, even in the absence of other evidence, the analogy cannot be regarded as a coincidence. Moreover, confirmatory evidence has been provided by frequent microscopic observation, in irradiated lesions of this kind, of lymphocytic destruction in every respect similar to that which was first observed and described by Heineke.

Leukocytic, and especially lymphocytic, infiltration is an early and prominent feature of most inflammatory conditions. Especially is this true in inflammations caused by bacterial infection. If it can be assumed that the leukocytes which the organism mobilizes around the site of infection represent an effort to localize the infection and get rid of the infectious material by phagocytosis or otherwise, it must be inferred that the infiltrating cells contain or elaborate within themselves the protective substances that enable them to neutralize the bacterial or other toxic products that give rise to the defensive inflammation. If these assumptions are well founded, it seems not unreasonable to deduce that irradiation, by destroying the infiltrating lymphocytes, causes the protective substances contained by such cells to be liberated and thus to be made even more readily available for defensive purposes than they were in the intact cells. All the circumstances surrounding the behavior of inflammatory lesions after irradiation are in harmony with this view. The same process also undoubtedly plays an

important part in the reaction of chronic inflammatory lesions, but in such cases the reaction is modified according to the degree of leukocytic infiltration on the one hand and to the amount of connective tissue on the other. This probably explains why the resolution and cure of chronic inflammations, such as those mentioned, require that irradiation be repeated at intervals for some time.

*Radiotherapy and the Genital Glands.*—The radiosensitiveness of the genital glands is important from more than one point of view. The relative ease with which testicular or ovarian function can be abolished by irradiation furnishes a simple method of accomplishing this result whenever such functional arrest is necessary or desirable. The method has seldom been applied to the male, but it is commonly employed in the female as an increasingly valuable method of treating hemorrhagic disturbances and fibromyoma of the uterus. Arrest of ovarian function indirectly causes atrophy of the uterus and of the fibroid tumors. In both the male and the female, roentgen rays or radium might well be utilized to castrate the feeble-minded, a method that would remove the objection to surgical operation. The danger of sterilization to professional radiologists and nonprofessional technical assistants has long been realized. Fortunately, modern methods of protection, if applied, remove all danger from such employment.

*Radiotherapy for Benign and Malignant Tumors.*—The specific sensitiveness of different kinds of cells constitutes the most important single factor in the treatment of neoplasms. The value of roentgen rays or radium in the treatment of tumors of different varieties depends mainly on this feature. The susceptibility of tumors to irradiation agrees closely with the radiosensitiveness of normal cells of the same kind as those from which the tumors are derived and of which they are largely composed. Thus, the inordinate hyperplasia of lymphoid structures that characterizes Hodgkin's disease, lymphosarcoma and lymphatic leukemia retrogresses under irradiation at the same rate as normal lymphocytes are known to be destroyed by similar exposure. In fact, so striking is the parallel that irradiation is now being used daily as a means of distinguishing such conditions when their clinical features do not permit absolute identification. In some cases, indeed, the radiotherapeutic method of diagnosis is more accurate and dependable than microscopic examination.

The only tumor that approaches lymphogranuloma or lymphoblastoma in susceptibility to irradiation is the embryonal carcinoma, or seminoma, of the testis, the radiosensitiveness of which corresponds to that of normal spermatogonial cells. This is the most common neoplasm affecting the organ. Heretofore it has often been mistakenly regarded as a variety of sarcoma. Primary and secondary growths of

this kind retrogress rapidly and some disappear completely, though seldom permanently, after irradiation. The rate of regression is not quite so rapid as that of lymphoid tumors, but next to that is more rapid than the rate of any other variety of tumor. The reaction of mixed, or teratoid, tumors of the testis is less rapid and seems to vary with the proportion of spermatogonial epithelium entering into their structure. The clinical features of testicular tumors and the path and elective sites of metastasis are usually so characteristic as to make confusion with lymphoid tumors all but impossible.

Knowledge of the relative radiosensitiveness of different cells has enabled Ewing and others to distinguish a group of bone tumors from other neoplasms that affect the skeleton. Ewing has designated this tumor as diffuse endothelioma of bone because endothelial cells are a prominent feature, but it is more widely known under the term endothelial myeloma applied to it by Kolodny and others. Unlike all other tumors of bone, the diffuse endothelioma of Ewing is exceptionally sensitive to radium and roentgen rays. Indeed, the exceptional susceptibility of this tumor to irradiation was one of the peculiarities that convinced Ewing that this variety of neoplastic disease is entirely different from osteogenic sarcoma. The rate at which such neoplasms retrogress after exposure to the rays suggests a more than coincidental relation to lymphogenous disorders, such as those observed in lymphoblastoma. The rate of regression of endothelioma so closely approximates that of lymphosarcoma or Hodgkin's disease that one is led to infer a definite relationship. At any rate, among tumors of bone the susceptibility is quite exceptional. The only other tumor of bone that can be said to be radiosensitive is chondrosarcoma, but the susceptibility of the latter variety is much less than that of the former. The difference is so great that confusion is practically impossible. Osteogenic sarcoma, on the contrary, can hardly be said to be radiosensitive. Rather, it is characterized by its resistance to irradiation. Few such tumors can be made to retrogress to an appreciable degree, even by the most intense irradiation. In fact, increasing experience with radiotherapy for tumors of bone makes it seem more and more likely that, whenever such a tumor proves unusually sensitive and diminishes rapidly in size or disappears temporarily or permanently after irradiation, it is an endothelioma, regardless of any classification based on microscopic appearance.

Another tumor of bone the radiosensitiveness of which is usually so characteristic as to constitute a valuable diagnostic sign is the so-called benign giant cell tumor. Two or three weeks after irradiation, the growth, instead of undergoing gradual retrogression for a time, or remaining unaffected, as do all malignant neoplasms of bone or soft tissues, begins to swell, and the swelling is accompanied by redness and



pain. This may continue for a number of weeks. If the patient or the attending physician has not been forewarned, he may quite naturally conclude that the rays have actually stimulated the tumor to increased growth, and this assumption may result in unnecessary sacrifice of the affected limb. After from three to six weeks, this acute reaction subsides spontaneously, and after the lapse of several months roentgenograms of the bone generally show deposition of fresh bone. In time, the entire tumor is replaced by solid bone. This kind of reaction differs entirely from the behavior of malignant tumors and supports the view that giant cell growths are chronic inflammatory lesions, at least at the outset. The fact that some of these tumors ultimately acquire malignant features does not affect the apparent validity of this deduction. All true tumors, benign as well as malignant, retrogress rapidly or slowly, remain stationary, or continue to grow at the same rate as before irradiation.

Many other examples might be mentioned, but these are sufficient to illustrate the important bearing on medical diagnosis and treatment of the radiosensitiveness of cells and tissues. Heretofore, for some reason, biologists have seldom made use of radiation for experimental purposes. As soon as they begin to realize its possibilities they will find in the method a means of acquiring much valuable information, and such increase in knowledge will help to extend the diagnostic and therapeutic applications.

# ENTEROSTOMY

## A CONSIDERATION OF THE LITERATURE

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### THE EARLIER LITERATURE

Enterostomy was recommended by Fuhr and Wesener in 1886 as a useful measure in the treatment for intestinal obstruction. For cases in which the obstruction was not readily relieved or the patient's condition did not permit an extensive operative procedure, its use was advised for temporary relief. A distended loop of intestine was brought up into the incision and sutured to the peritoneum.

The use of this measure was quite widespread from 1880 to 1900. The technic was that described or it varied in that the loop was brought out to the skin, or it consisted of either of these methods with the addition that a glass tube was fastened into the intestine.

The apparent success of this form of treatment in cases of mechanical ileus suggested its possible value in certain cases of appendicitis. It was noted that in some cases of appendicitis there was marked distention, and that in others following the operation for appendicitis great distention occurred. The mortality was very high in these two groups of cases.

Porter, in 1897, reported a case in which he performed enterostomy for the distention associated with appendicitis, with recovery of the patient. (For additional early references to enterostomy in the United States see references to Hadra and Henrotin.) Heidenhain's papers, published in 1902, in which he reported five cases in which enterostomy was done for ileus following operation for appendicitis, with four recoveries, are quoted in the German literature as the inception of this measure as a generally accepted procedure. Lund, in 1903, reported five cases with four recoveries. Tinker, Bullitt, Dunsmore and Porter, in their discussions on Lund's paper, stated that they considered this procedure a life-saving measure which they had used to a limited extent.

Thomas is the only person whose objections to this measure were found in the literature of this period. He stated that he considered

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This is a preliminary paper which is to be followed by a statistical consideration of the subject.

that those patients who recovered after an enterostomy would have done so without the operation. He quoted Nicholas Senn as teaching the same belief.

Broca appears to be the first in the French literature to have recommended the use of enterostomy for intestinal obstruction following appendicitis. His paper was published in 1901, and a case with recovery was reported.

Following Heidenhain's papers, the use of enterostomy became quite widespread in Germany. Gebhardt, in 1904, recommended its use not only in the treatment of postappendical obstruction but as a prophylactic measure in certain cases of appendicitis. In the discussion of appendicitis and peritonitis at the German Surgical Congress in 1909, enterostomy was recommended by Barth, Alapý and Hoffmeister. Krogus, in 1911, reported seventy cases in which he had performed the operation between 1900 and 1911 with twenty-three recoveries.

In 1921, Brunner reported thirty-four cases with ten recoveries; Wortmann, twenty-seven cases with twenty-two recoveries; Dubs, twenty-four cases with six recoveries. Eliot and Pickhardt, in 1921, reported four cases in which ileostomy had been done for obstruction following appendicitis in 1907, with three recoveries.

Sick, in 1908, and again in 1909, published articles in which he questioned whether or not the efficacy of this measure had been proved.

From 1921 on, particularly from 1925 to 1928, papers on enterostomy occur very frequently in the literature of Germany, Italy, France, Great Britain and the United States. A representative list of these will be found at the end of the paper.

With almost no exception the procedure is recommended. In a great many of the papers no cases or statistics are cited to back up the recommendation, the reason usually cited being that some other surgeons thought it a successful form of treatment. Many others cite from one to ten cases in which all or part of the patients recovered. None of them give any suggestion of a method for determining which of the patients who recovered might have been expected to survive without enterostomy.

The few criticisms found in the literature other than those already mentioned will be taken up later.

#### EXPERIMENTAL RESULTS

Before entering into a further consideration of the literature on enterostomy, it might be well to review briefly the results of some of the experimental work on intestinal obstruction and peritonitis.

McClure, in 1907, showed that the stagnant contents of obstructed loops form an excellent culture medium which soon becomes loaded with bacteria. The bacterial content could be slight at the time of

closure, but multiplication was extremely rapid. This rich bacterial growth not only provided the gas which damaged the bowel by over-distention but also invaded the strangulated tissues causing septic gangrene. McClure thought that there was no absorption until the intestinal wall was damaged.

Albeck, in 1901, Murphy and Brooks, in 1915, and many other observers since, recognized the occurrence of a toxic substance within the bowel but emphasized the fact that absorption of the toxin did not occur through the normal intestinal epithelium. Davis, in 1914, and Schonbauer, Stone, Whipple and Wilkie later demonstrated that large amounts of this toxin may be introduced into the lumen of the normal small intestine with no untoward results.

L. R. Dragstedt, Moorehead and Burcky, in 1917, found that closed loops of the jejunum were fatal within from three to four days. If the isolated loop, instead of being closed, was washed and left open into the peritoneal cavity, those dogs that survived the peritonitis remained well. In a few weeks the loop was found to be sterile and was then closed without causing toxic symptoms, although the loop became distended and in some cases even ruptured. In these sterile loops, when the blood supply was entirely occluded, anemic necrosis developed. In the absence of bacteria this process caused no toxemia.

L. R. Dragstedt, C. A. Dragstedt, McClintock and Chase, in 1919, found that washing the closed loop with ether, alum or tannic acid so affected the loop that it would not absorb the toxic products, but that bacterial action went on unchanged.

Gerard, in 1922, stated that the contents of an obstructed bowel become poisonous as a result of the formation of histamine and allied proteolytic products by the action of putrefactive bacteria.

Haden and Orr, in 1923, reported that they were able to keep dogs with pyloric or intestinal obstruction alive for from twenty to thirty days by the hypodermic administration of sodium chloride solution.

Gamble and Ross, in 1925, found the cause of death in pyloric obstruction to be the loss of sodium and chloride ions by vomiting. This loss resulted in the inability of the body tissues to retain water. The resulting dehydration combined with starvation caused the death of the dogs. The authors found that the treatment with saline by hypodermoclysis, intravenously or through an enterostomy opening, kept the dogs alive.

Orr and Haden, in 1926, reported that in the dog they found that the chemical changes in the blood characteristic of acute obstruction of the jejunum are not prevented by jejunostomy. They found no beneficial effect on the duration of life. Sodium chloride solution tended to prolong life in acute obstruction of the jejunum with or without jejunostomy. Simple jejunostomy killed the animals quicker than the obstruction.

The same authors, in 1929, reported the same chemical changes in the blood in peritonitis as those found in intestinal obstruction, i. e., an increase in nonprotein and urea nitrogen, a decrease in chlorides and no constant change in the carbon dioxide-combining powers.

Experimental peritonitis without treatment was fatal in their first series in three and one-eighth days; in their second series, in four and one-eighth days. When treated with ileostomy plus 40 cc. of a 1 per cent solution of sodium chloride per kilogram of body weight, the average life was extended to ten and one-third days. With ileostomy alone, they reported no lengthening of life.

In 1926, they reported that drainage of the jejunum in dogs caused death in from two to five days, even though the fluids and chlorides lost were replaced in some manner. Drainage of the ileum 6 inches (15.2 cm.) above the cecum was found compatible with life in dogs for several weeks. They concluded from these experiments that enterostomy (in the ileum) should be done when the symptoms of obstruction appear with peritonitis in the lower part of the abdomen, provided the intestine above shows signs of peristaltic action. In case of doubt they recommended enterostomy as it does no harm and may do good. They stated that in addition large quantities of saline should be used.

Hausler and Foster, in 1924, came to the following conclusions in experimental intestinal obstruction:

"Experimental intestinal obstruction may be classified as acute simple obstruction and acute strangulation obstruction. The pathology and lethal factors are definitely different in the two classes." In the first class they found only slight changes in the pulse, temperature, respiration and blood pressure. In the second class they found profound changes in all of these factors. They stated that from 30 to 40 per cent of cases of acute ileus belong to the first class, but that if they are neglected they go to the second class.

Hartwell and Cooper, in summing up the experimental work on the toxemia of intestinal obstruction, stated:

(1) In high obstruction there are two different processes involved. First, there is a profound disturbance in the acid-base mechanism resulting in alkalosis and dehydration. Secondly, there is a definite toxemia. In simple obstruction this first process is the more prominent and often fills the whole picture. However, toxemia may enter also to a varying extent. On the other hand, in closed loops and strangulation the toxemia is on the ascendancy and often crowds everything else out.

(2) There is a toxin in the lumen of the obstructed gut and it looks very much as though it reached the blood stream and was responsible for the toxemia. The origin of this toxin is not entirely clear. Those who say that it is formed by bacteria must show:

(a) Why high obstruction is more fatal than low.

(b) Why the toxin appears so rapidly after obstruction.

(c) Why the toxin appears in the gut immediately after toxic injection.

(d) Why the toxin appears in such conditions as clotting of the portal vein, acute pancreatitis and bilateral adrenalectomy, where there is no obstruction.

Those who claim that it is not formed by bacteria have to prove its formation in their absence.

(3) There seems to be some mysterious connection between the toxemia of high obstruction, acute pancreatitis, bilateral adrenalectomy and anaphylaxis.

. . . We should like to emphasize the fact that more work should be done on strangulation. Here we have the toxemia developed to the highest degree. We are able to control the alkalosis and dehydration. However, it is very rare to see simple obstruction in the clinics without the complication of toxemia. Therefore, it remains to find a means of combatting this dread condition.

They have appended to their discussion a very comprehensive list of references on the experimental work done with intestinal obstruction.

#### EMPTYING THE BOWEL AT OPERATION

From a consideration of part of these experimental results it is easy to arrive at the conclusion that the obstructed loop or loops should be emptied as promptly as possible. Some men go even a step farther and conclude that the contents should be removed from the patient at the time of the operation. These men do not take into account the experimental finding that the toxins apparently are not absorbed through normal intestinal mucosa.

Stone recommended that the contents of the bowel be removed at the time of operation and that the intestine be freely irrigated with large quantities of distilled water. He cited no clinical material or statistics to back up his recommendation.

Holden advised emptying the bowel at the time of operation, and then closing the opening through which it was emptied. He used a flanged glass tube for emptying the intestine. He stated that his mortality figures in intestinal obstruction had been lowered 10 per cent by this practice.

Cornils, in 1926, described a very complicated apparatus for emptying the intestine at operation. Cambresier advised the puncture and drainage of the intestine or enterostomy as the treatment for post-operative paralytic ileus. Willis advised in some cases of obstruction that the bowel be punctured, drained and the opening then closed.

Flörcken gave comparative figures which are most interesting in a consideration of this emptying operation (table 1).

He concluded that emptying at the time of operation should not be done, but that enterostomy was of value when the intestine showed contractility. He did not state whether or not the emptying was done on the worst cases, which of course is a possibility and would remove some of the teeth from his argument.

ILEOCOLOSTOMY, JEJUNOCOLOSTOMY AND CECOSTOMY IN  
PERITONITIS

While ileostomy and jejunostomy were being tried out as forms of treatment for ileus following operations for peritonitis, another mechanical treatment was suggested by Sampson-Handley in 1915 and again in 1916. He advised jejunocolostomy to short-circuit the involved area and with this a cecostomy to drain the obstructed cecum and terminal ileum. He thought jejunostomy was inadvisable.

Nyulasy, in 1917, recommended cecostomy alone as the treatment for intestinal paralysis subsequent to operations for peritonitis. He felt that the stasis was not complete. Roeder believed that in operations for appendicitis with peritonitis, when the cecal region is thickened and indurated, that region should be side-traced by doing an ileosigmoidostomy. He reported twenty-one such operations with twenty recoveries. Deaver likewise recommended that, when the terminal ileum and cecum

TABLE 1.—*Data of Flörcken*

	Cases	Died	Mortality, per Cent
Strangulation ileus .....	41	7	17
Emptied at operation.....	7	4	57
Not emptied .....	34	3	9
Volvulus, invagination, gallstone ileus, etc.....	17	8	47
Emptied at operation.....	4	4	100
Not emptied .....	13	4	30

are found indurated when operating for an appendical abscess, either an ileocolostomy or ileocecostomy be done.

Voncken advised that in obstructions following operations for acute appendicitis a cecostomy be done if the cecum is found distended. However, in three of his cases cecostomy gave no relief, and ileostomy was performed the following day. Two of these patients recovered.

Duncombe advised ileocolostomy combined with the use of hypertonic salt solution intravenously. He reported recovery in one case after this treatment.

ENTEROSTOMY IN MECHANICAL ILEUS

The use of enterostomy as a useful adjunct in the treatment for mechanical ileus has been more or less accepted in the literature since 1880. From 1910 on, this became somewhat limited to jejunostomy although ileostomy was also recommended frequently.

Between 1920 and 1925, jejunostomy was advised in the treatment for mechanical ileus by C. H. Mayo, Wilkie, Taylor, Walker, Summers, Lee and Downs, and Delore. Mallet-Guy and Creyssel. This list is given only as representative of the large literature on the subject.

## JEJUNOSTOMY IN PERITONITIS

While the teaching of enterostomy, but more particularly of ileostomy as treatment for ileus and peritonitis was spreading gradually from the original recommendation of Heidenhain, Victor Bonney came out in 1910 with a very definite recommendation that jejunostomy be used instead. In 1916, he wrote: "I hold strongly that all cases of paralytic obstruction whether primary or secondary to an organic obstruction or to peritonitis, when advanced to the stage of fecal vomiting, should be treated by jejunostomy. The effect in many cases has been remarkable."

Papers in addition to those specifically mentioned in which jejunostomy and ileostomy are discussed and recommended are listed at the end of this article.

Its success in the treatment for mechanical obstruction developing from two to twenty days after operation for the peritonitis of appendicitis or other causes appears quite general in these reports. Ordinarily the obstruction disappears as the inflammatory processes subside, and in those cases in which the obstruction is due to a band or other cause not spontaneously relieved the patient is carried through the critical time, and the obstruction can then be relieved with the patient in condition to withstand the operation.

## PARALYTIC ILEUS

In the paralytic type of ileus various authors report good results with jejunostomy, although the majority qualify this with the limitation that the jejunum must show active peristalsis. Here, of course, the reported cases are subject to question, not as to cure but as to the classification of the type of ileus. Wilkie, in 1928, stated that a postmortem study of a series of patients dying from so-called peritonitis or paralytic ileus from five to ten days after operations for acute appendicitis showed the cause of death to be mechanical intestinal obstruction in 75 per cent. This suggests that those cases of paralytic ileus in which jejunostomy was successful were in reality cases of mechanical ileus. But, possibly, this further suggests that one cannot clinically separate mechanical and paralytic ileus after operations for peritonitis and that one should give the patient the benefit of the doubt and a jejunostomy.

## MEDICAL TREATMENT FOR POSTOPERATIVE ILEUS

The close observation and study of the patients making up any large series of cases of peritonitis will reveal a considerable number of patients who have a partial paralytic ileus or a temporarily complete one, who recover without additional surgical procedures. The question may be brought up as to whether or not those patients successfully treated by enterostomy do not belong to this class now under discussion.



Of course, the remarkably rapid and complete recovery of these patients, who before operation appeared in extremis, is given as the answer to this question, but this is not as conclusive as statistics would be.

This brings one to the medical treatment for postoperative ileus. This has not been given the consideration due such an important subject, although a great deal of medical treatment for postoperative ileus is done without the physician stopping to realize that that is what he is treating.

It is very difficult to draw the line between the nausea and distention due to ether, to handling of the intestine, to the irritation of peritonitis or other similar temporary cause and that of beginning ileus. In fact, they are probably one and the same thing.

The medical treatment includes stomach lavage, spinal anesthesia in the spastic paralysis, anal dilatation, pituitary extract, atropine, morphine, sodium chloride, dextrose, water and the use of the rectal tube and flaxseed poultices. As the patient becomes more ill, one must add the use of camphor, caffeine and other stimulants.

The Einhorn tube and the duodenal bucket have been used with success. The more recent addition of the Levine tube has made the treatment much simpler and surer. It may be put down, left in place, and then irrigated every hour or half hour with physiologic solution of sodium chloride. Gastric dilatation is prevented, the upper part of the intestine is emptied by reverse peristalsis and undoubtedly some water and salt are supplied to the patient. Additional operation is often averted in this manner. This is recommended by Jancke and others.

J. H. Woolsey stated that the duodenal tube will accomplish all that jejunostomy does. Likewise, Romano and Rey reported the successful use of the duodenal tube instead of ileostomy or jejunostomy in treatment for the uncontrollable vomiting of bacterial peritonitis.

Sick, in 1908, doubted whether primary enterostomy was of value in intestinal obstruction and volvulus. In 1909, he added to this that he felt the treatment for peritonitis by primary enterostomy was of very questionable value. He considered early diagnosis and operation followed by the various medical treatments of much greater value in reducing the mortality figures. He felt that the inanition, additional shock, possibility of infection and necessity of closing the fistula contra-indicated enterostomy in purely mechanical obstruction.

Eisberg considered jejunostomy as contraindicated in mechanical ileus, stating that it causes death, and if the patient recovers a secondary operation is necessary.

#### SURGICAL TREATMENT FOR POSTOPERATIVE ILEUS

However, cases will be found in which medical treatment, even including the thorough and proper use of the Levine tube, will give no

relief. A considerable percentage of these cases will be due to mechanical obstruction. Operative intervention as soon as diagnosis is made and other treatments fail will give a high percentage of recoveries. If the patient's condition and the nature of the obstruction permit, removal of the cause is indicated. Otherwise a jejunostomy should be done. A later relief of the mechanical obstruction may be necessary in a few of these cases.

The generally accepted manner of doing the jejunostomy at the present time appears to be as follows:

Under local anesthesia, a short incision is made in the left upper quadrant lateral to the rectus muscle. The loop of small intestine immediately beneath the incision is brought up into the incision. The time and trauma involved in locating definitely a loop of jejunum are rarely justified.

The end of a large-sized soft rubber catheter is fixed in the lumen of the intestine either by two purse-string sutures or by the Witzel method. The catheter is then drawn through a small hole in the omentum and the omentum drawn up against the parietal peritoneum. The wound is closed about the catheter in layers, or if the patient's condition is precarious, may be closed with through-and-through sutures.

If the jejunostomy or ileostomy is done at the same time as another operation, the same procedure is used in inserting the catheter and bringing it through the omentum. A small stab wound is then made to the left of and above the umbilicus, and the catheter is then drawn out through this wound.

When the jejunostomy is done, it must not be left to cure the patient unaided. Irrigation should be done every hour or half hour with physiologic solution of sodium chloride. Salt and dextrose solutions should be given in large quantities by infusion or hypodermoclysis. Other treatments should be used as the indications arise.

As soon as clear contents without odor replace the turbid foul return which is obtained at first, and the distention is relieved, the tube is clamped and used for the introduction of salt solution and if necessary for nutrition. From the fourth to seventh day the tube will come away, and by the tenth to fifteenth day the sinus tract will close.

The remainder of the patients under consideration compose the group with paralytic ileus. If the condition is advanced and complete, even with jejunostomy the mortality is high. Whether or not jejunostomy lowers the death rate is a question and many authors feel that it is of no benefit. Most of those who do recommend it qualify this with the reservation that the jejunum must show contractility.

The evaluation of the results of jejunostomy in this class of cases is extremely difficult. First, there is the doubt as to the correct diagnosis; and, second, how can one be sure that those patients who recover would not have done so without enterostomy; and, furthermore, that some of those not surviving might have done so without the enterostomy.

I feel that at present no figures or statistics are available to argue for or against this form of treatment of ileus, but that the indications are, that if one can be certain he is not dealing with a mechanical ileus, enterostomy is probably of little use.

#### PRIMARY OR COMPLEMENTAL ENTEROSTOMY

Opinions as to the value of complementary enterostomy can be cited, but facts and figures are a different thing. The following is typical of the unlimited recommendation of enterostomy not backed by any statistics. Holman stated:

Ileostomy or enterostomy is indicated in severe cases of ruptured appendix with spreading peritonitis, in intestinal obstruction, peritonitis due to ruptured viscus or perforated bowel, postoperative ileus, traumatic peritonitis, pneumococcic or streptococcic peritonitis and in certain cases of intestinal anastomosis or resection of the bowel.

McKinnon, in 1928, stated that he not only treats patients with postoperative ileus by jejunostomy but does it at the time of operation in those cases in which ileus is expected to develop. He gives no statistics as to the decreased occurrence of postoperative ileus since starting this usage.

Clute stated:

Peritonitis gives paralysis of the involved gut and the result simulates obstruction because the loops above cannot empty.

He concluded from his own cases that:

Enterostomy in acute intestinal obstruction is of great value when it removes the toxic products collected above the point of obstruction. Drainage of the large intestine in low obstruction gave excellent results. Drainage of the jejunum in acute obstruction gave good results. Septic peritonitis produces death largely from toxemia arising from the infection plus the products of the intestinal obstruction caused by the paralysis of the gut. Caecostomy in peritonitis gave very poor results; jejunostomy quite satisfactory results. Jejunostomy should be added to our present methods for the treatment of diffuse septic peritonitis.

Whipple stated in 1927 that:

In dynamic ileus and paralytic ileus with peritonitis—where much distention of the small intestine and fecal vomiting are present—high ileostomy or jejunostomy is a life-saving measure. . . . An increase in enterostomies of 63 per cent gave a 13.2 per cent reduction in mortality.

He referred to a paper to be published later by Van Beuren and Smith (August, 1927). Comparative statistics on operation for ileus before and after 1900, as quoted by these authors, are shown in table 2.

The reductions in mortality would be readily accounted for by improvement in surgical technic and hospital regimen. The great increase in enterostomies performed, nearly double, should have resulted in a great decrease in the total mortality if it is the life-saving measure that it has been reported to be.

Comparison of mortality figures in peritonitis and obstruction operations in groups with enterostomies and those without always gives lower mortality in the groups not including enterostomies. The argument raised against this is that enterostomy is always saved as a procedure of last resort.

The only method of final evaluation for enterostomy would be to compare the mortality statistics in peritonitis and ileus obtained from

TABLE 2.—*Data of Van Beuren and Smith \**

	Number of Cases		Mortality Percentage	
	Series 1900	Series 1925	Series 1900	Series 1925
Entire series .....	1,000	1,089	43.2	41.8
Nonenterostomy group .....	810	740	32.2	33.0
Enterostomy group .....	190	349	64.2	60.7

\* One thousand cases compiled by C. D. Gibson, 1900; 1,089 cases compiled by Van Beuren and Smith, 1925.

various hospitals, comparing the figures from hospitals in which the staff does few or no enterostomies with the figures from those hospitals in which it is used as a routine measure.

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# ACUTE PANCREATITIS

## REPORT OF SIXTY-FOUR CASES

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This study is based on all the available records of patients with acute pancreatitis who were treated by members of the Chicago Surgical Society.<sup>1</sup>

The following classification has been found satisfactory:

- A. Acute idiopathic pancreatitis
  - 1. Simple edematous or nonhemorrhagic pancreatitis
  - 2. Hemorrhagic pancreatitis
  - 3. Necrotic or gangrenous pancreatitis
  - 4. Suppurative pancreatitis
- B. Acute pancreatitis associated with malignancy
- C. Acute pancreatitis following trauma

Fitz<sup>2</sup> classified acute pancreatitis into hemorrhagic, suppurative and gangrenous. Brocq<sup>3</sup> classified it as aseptic and infected. He included four degrees of aseptic pancreatitis: acute hemorrhagic, edematous, sub-acute encysted and attenuated. Brocq considered gangrenous pancreatitis as infected with anaerobic, and the suppurative type as infected with pyogenic, bacteria.

In 1856, Bernard<sup>4</sup> reported the production of an acute hemorrhagic pancreatitis following the experimental injection of bile and sweet oil

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Read in abstract before the Chicago Surgical Society, May 2, 1924, and discussed, March 6, 1931.

1. Case reports from members of the Chicago Surgical Society. No cases are included after May, 1924. The cases were reported by: Edmund Andrews, Arthur D. Bevan, Carl Beck, E. J. Brougham, Gatewood, John A. Graham, W. T. Harsha, Harry Jackson, Charles E. Kahlke, Allen B. Kanavel, Dean D. Lewis, R. W. McNealy, G. L. McWhorter, Carl Meyer, Edwin M. Miller, Paul Morf, O. E. Nadeau, John Nuzum, A. J. Ochsner, Nelson M. Percy, D. B. Phemister, H. M. Richter, H. M. Riebel, C. C. Rogers, Charles F. Sawyer, William Schroeder, V. C. Schrager, Joseph Smith, D. C. Straus, George de Tarnowsky, Roger T. Vaughan and John A. Wolfer.

2. Fitz, R.: Acute Pancreatitis, M. Rec. **35**:197, 1889.

3. Brocq, P.: Les pancréatites aiguës chirurgicales, Paris, Masson et Cie, 1926.

4. Bernard, Claude: Mémoire sur le pancréas, Compt. rend. Acad. d. sc., 1856, supp. 379.

into the pancreatic duct, with death after eighteen hours. Many other substances produced similar results.

Considerable progress has been made through experimental study and by more general clinical recognition of acute pancreatitis, but owing to its infrequent occurrence and to the relatively difficult diagnosis, little progress has been made in reducing the incidence or in lowering the mortality due to this highly fatal condition.

The following classification of the etiology of acute pancreatitis may be advocated.

*A. Infectious origin*

1. By extension along the lymphatics
2. By extension from the blood stream
3. By extension along the pancreatic ducts from the duodenum or from the bile tracts
4. By direct extension from infected foci
5. Following activation of bacteria in the normal gland
6. By bacterial permeability from adjacent altered viscera

*B. Noninfectious origin*

1. Mechanical, including stasis in the ducts
2. Chemical and originating in activated ferments, resulting from
  - (a) Bile
  - (b) Duodenal contents
  - (c) Degenerated duct contents
  - (d) Autolysis
3. Degenerative changes in the pancreas
  - (a) Secondary to benign or malignant tumors
  - (b) Resulting from vascular degeneration or hemorrhage
  - (c) Toxic changes following systemic disease
4. Trauma

*C. A combination of two or more of the factors*

Infection, either directly or indirectly, may be a factor in acute pancreatitis (Barling<sup>5</sup> and Wolfer<sup>6</sup>). The bacteria found most frequently include the colon bacillus, the pneumococcus and the staphylococcus. While Brocq found anaerobic bacteria in the gangrenous type of acute pancreatitis, he found that the necrotic and subacute types were sterile.

Truhart<sup>7</sup> collected eighty records of careful bacteriologic examinations in cases of acute pancreatitis. No bacteria were found in forty-three instances, while in thirty-seven cases bacteria were obtained from

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5. Barling, G.: An Address on Pancreatitis and Its Association with Cholecystitis and Gallstones, *Brit. M. J.* **1**:705, 1923.

6. Wolfer, J. A.: Practical Points in Diagnosis and Treatment of Acute Pancreatitis, *Illinois M. J.* **41**:14 (Jan.) 1926; recent unpublished paper.

7. Truhart, H.: Pankreas-Pathologie: Multiple abdominale Fettgewebsnekrose, Weishaden, J. F. Bergmann, 1902; quoted by Opie, E. L.: Diseases of the Pancreas, Philadelphia, J. B. Lippincott, 1910.

the pancreas, the peritoneal fluid or from foci of necrosis. Numerous micrococci were found ten times, bacilli, mostly colon bacilli, twenty-two times, and unidentified organisms in the other cases. In acute necrosis of the pancreas, Jones<sup>8</sup> was unable to find bacteria in smears or cultures.

Experimentally, Carnot,<sup>9</sup> Hlava,<sup>10</sup> Körte<sup>11</sup> and others have been able to produce hemorrhagic, suppurative and sclerosing types of pancreatitis by injecting into the duct colon, pyocyaneous and other bacteria. Archibald and Brow<sup>12</sup> after injecting the colon bacillus, observed a very fatal type of acute pancreatitis. Kemp<sup>13</sup> stated that certain bacteria, especially of the typhoid and colon group, are capable of activating the proteolytic pancreatic enzymes.

The lymphatic route of infection from the gallbladder, liver and the appendix has been emphasized in both acute and chronic pancreatitis (Graham and Peterman<sup>14</sup> and Barber<sup>15</sup>), but the acute type has not been produced experimentally by this route (Jones). The lymphatics of the pancreas have been shown by numerous writers to anastomose freely with those of the surrounding viscera, especially with those of the duodenum and gallbladder. Franke<sup>16</sup> has injected the lymphatics about the head of the pancreas from those of the gallbladder, which has been considered the chief source of infection by Maugeret,<sup>17</sup> Arnsperger,<sup>18</sup> Deaver,<sup>19</sup> Graham, Judd<sup>20</sup> and Griffiths.<sup>21</sup>

8. Jones, F.: *S. Clin. North America* **2**:1125 (Aug.) 1922; *Acute Pancreatitis*, Boston M. & S. J. **186**:337, 1922.

9. Carnot, P.: *Maladies des glandes salivaires et du pancréas*, Paris, J. B. Baillière et fils, 1908, p. 109.

10. Hlava, quoted by Opie (footnote 7).

11. Körte, W.: *Cong. de la Soc. internat. de chir.*, Bruxelles, Sept. 1911; quoted by Brocq (footnote 3).

12. Archibald, E., and Brow: *The Experimental Production of Pancreatitis in Animals as the Result of the Resistance of the Common Duct Sphincter*, *Surg., Gynec. & Obst.* **28**:529 (June) 1919.

13. Kemp, R. C.: *Diseases of the Stomach and Intestines*, ed. 3, Philadelphia, W. B. Saunders Company, 1917.

14. Graham, E. A., and Peterman, M. G.: *Further Observations on the Lymphatic Origin of Cholecystitis, Choledochitis and Associated Pancreatitis*, *Arch. Surg.* **4**:23 (Jan.) 1922.

15. Barber, H.: *New York State J. Med.* **22**:543, 1922.

16. Franke: *Deutsche Ztschr. f. Chir.* **111**:539 (Sept.) 1911; **54**:399, 1900.

17. Maugeret: *Thèse de Docteur*, Paris, 1898, quoted by Archibald, E.: *Internat. Clin.* **2**:1, 1918.

18. Arnsperger: *München. med. Wchnschr.* **68**:729, 1911.

19. Deaver, J.: *Pancreatic Lymphangitis*, *Surg., Gynec. & Obst.* **28**:433 (May) 1919; *Pancreatitis*, *S. Clin. North America* **1**:1, 1921; *Ann. Surg.* **68**:281, 1918.

20. Judd, E. S.: *The Relation of the Liver and the Pancreas to Infection of the Gallbladder*, *J. A. M. A.* **77**:197 (July 16) 1921.

21. Griffiths, H. E.: *Lancet* **2**:203, 1904.

In 1,290 cases of gallbladder disease, Judd found an associated chronic pancreatitis in 26.8 per cent. Mayo-Robson<sup>22</sup> found changes in the pancreas in 60 per cent of cases with gallstones, and Quenu and Duval<sup>23</sup> found changes in 50 per cent. Jones believed that chronic pancreatitis was an inflammation of the interstitial tissue frequently occurring by way of the lymphatics, while acute pancreatitis was an involvement of the parenchymal cells occurring by way of the ducts.

Infection may be carried to the liver from the gastro-intestinal tract by the portal system and produce pancreatitis by a descending infection as believed by Stockton.<sup>24</sup> The hematogenous route of infection may produce acute pancreatitis either by bacterial metastases or by extension along the blood vessels, as thrombophlebitis, from the foci of infection.

As a sequel to epidemic parotitis, the occurrence of acute pancreatitis has been recognized for a long time (Oser<sup>25</sup>). Farnham<sup>26</sup> and Edgecombe<sup>27</sup> have reported cases complicating mumps. Farnham collected 119 cases. The disease occurred more often in boys and young men, and occasionally preceded the parotitis.

Experimentally, Rosenow<sup>28</sup> injected intravenously a streptococcus obtained from the tonsils of a patient having symptoms of inflammation of the gallbladder and pancreas, and obtained lesions in those organs, although with other strains of streptococci lesions of the pancreas were rare.

Extension of infection may occur along the chief pancreatic duct from the bile tracts or from the duodenum directly up either pancreatic duct. Downward infection from the bile by direct reflux into the pancreas may occur. Infection may also occur from a focus in the duodenum, and extend up either pancreatic duct or, possibly, by a reflux of duodenal contents.

It is probable that stasis in the pancreatic duct, either alone or together with a reflux of bile into the duct is a contributing factor to the development or extension of infection in the pancreas. Direct extension of infection from adjacent foci may result from various types of acute inflammation.

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22. Mayo-Robson: *Lancet* **1**:773, 1904.

23. Quenu and Duval: *Rev. de chir., Paris* **32**:401, 1905.

24. Stockton: *Gastrointestinal Infection in Relation to Infection of the Liver and Bile Passages*, *Am. J. M. Sc.* **163**:485 (April) 1922.

25. Oser, L., in Nothnagel: *Encyclopedia of Practical Medicine*, Philadelphia, W. B. Saunders & Company, 1905.

26. Farnham, L. W.: *Pancreatitis Following Mumps*, *Am. J. M. Sc.* **163**:859 (Oct.) 1922.

27. Edgecombe: *Practitioner* **80**:194 (Feb.) 1908.

28. Rosenow, E. C.: *Focal Infection and Elective Localization of Bacteria in Appendicitis, Ulcer of the Stomach, Cholecystitis and Pancreatitis*, *Surg., Gynec. & Obst.* **33**:19 (July) 1921.

Bile (Tatum<sup>29</sup>) or intestinal contents, such as from a perforated duodenal ulcer (Richter<sup>30</sup>), may produce an acute pancreatitis. Bacteria may be present in the normal liver and pancreas, as was shown in animals by Tower<sup>31</sup> and Dragstedt.<sup>32</sup> Tower was unable to produce a sterile pancreatitis. Patrie, Pyle and Vale,<sup>33</sup> after a direct anastomosis of the pancreatic duct, experimentally, with both the small and large intestine, found no ascending infection in the pancreas.

Bacterial permeability of adjacent altered viscera may be a source of infection in the pancreas. Such an extension of infection may occur primarily or secondarily after acute changes or necrosis have occurred from bile or chemical changes. The permeability of the intestine to bacteria in acute intestinal obstruction was demonstrated by McClure,<sup>34</sup> who found bacteria quite early in the peritoneal cavity in 45 per cent of cases of experimental obstruction of the colon and in 28 per cent of those of obstruction of the small intestine. Moynihan<sup>35</sup> noted in acute pancreatitis that there was usually a local dilatation and inflammation of the segment of transverse colon below the pancreas.

An abscess or peritonitis has been observed following nonperforative appendicitis, especially after catharsis (McWhorter<sup>36</sup>). Permeability of the intestine to bacteria has been observed under conditions such as those in typhoid fever. The production of a septic peritonitis by *Bacillus welchii* following the intraperitoneal injection of sterile bile and salt solution has been demonstrated by Rewbridge.<sup>37</sup>

Andrews and Hrdina<sup>38</sup> demonstrated that there was a substance in bile besides the salts that renders a change in the permeability of the bowel wall so that anaerobic bacilli may pass through and produce peritonitis with a rapid toxemia. These authors reported anaerobic

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29. Tatum: *J. Biol. Chem.* **27**:243, 1916.

30. Richter, H. M.: *Perforating Duodenal Ulcer with Fat Necrosis*, Northwestern Univ. M. School Bull., Dec., 1910.

31. Tower, L. E.: *The Pathologic Physiology of Experimental Gangrenous Pancreatitis*, *J. A. M. A.* **86**:1112 (April 10) 1926.

32. Dragstedt, L. R.: Unpublished report. Ellis, J. C., and Dragstedt, L. R.: *Liver Autolysis in Vivo*, *Arch. Surg.* **20**:8 (Jan.) 1930.

33. Patrie, Pyle and Vale: *Surg., Gynec. & Obst.* **24**:479, 1917.

34. McClure, R. D.: *An Experimental Study of Intestinal Obstruction*, *J. A. M. A.* **49**:1003 (Sept. 21) 1907.

35. Moynihan, Berkeley: *Ann. Surg.* **81**:132 (Jan.) 1925.

36. McWhorter, G. L.: *Non-Perforative Appendicitis Followed by Peritonitis or Abscess*, *Illinois M. J.* **40**:109 (Aug.) 1921.

37. Rewbridge, A. G.: *The Etiological Rôle of Gas-Forming Bacilli in Experimental Bile Peritonitis*, *Surg., Gynec. & Obst.* **52**:205 (Feb.) 1931.

38. Andrews, E., and Hrdina, L.: *The Cause of Death in Liver Autolysis*, *Surg., Gynec. & Obst.* **52**:61 (Jan.) 1931. Andrews, E.; Rewbridge, A. G., and Hrdina, L.: *Causation of B. Welchii Infection in Dogs with Sterile Liver Extract and Bile Salts*, *Proc. Soc. Exper. Biol. & Med.* **28**:136, 1930.

bacteria in the normal muscle of animals, with the production of gas gangrene by the injection of sterile bile salts and liver extract.

While pancreatitis may occur without infection, it may develop rapidly in the presence of bacteria from the normal gland or from an increased permeability of the bowel wall in the vicinity. A predisposition to extension from the intestine may be furthered by early local paralysis with ileus or by the presence of bile products in the congested pancreas.

#### NONINFECTIOUS ORIGIN OF PANCREATITIS

Acute pancreatitis may occur from mechanical, traumatic, chemical, enzymatic or degenerative factors, without infection. Although most authorities support the infectious origin, especially that arising secondary to inflammation of the gallbladder, statistics show that only about one half of the cases are associated with acute cholecystitis, gallstones or evident foci of infection.

Toxic products may develop within the pancreas, or they may be regurgitated into the pancreatic ducts from the biliary tract or from the duodenum. Inactive pancreatic juice is ordinarily harmless within the pancreas, and experimental ligation of the ducts usually will not produce necrosis, although Eggers<sup>39</sup> obtained an acute pancreatitis when they were ligated at the height of digestion. Cutting of the pancreatic ducts with the escape of the inactivated juices into the peritoneal cavity is unaccompanied by necrosis or clinical symptoms (Senn<sup>40</sup> and Flexner<sup>41</sup>). Simple injury to the pancreas usually fails to produce necrosis, although it may liberate an activating substance. Levin<sup>42</sup> has shown that crushing of the gland when associated with occlusion of the blood vessels may produce characteristic hemorrhagic necrosis. Clinically, trauma of the pancreas has rather frequently been followed by acute pancreatitis and also by pseudocysts (Primrose<sup>43</sup>).

Lee and Adair<sup>44</sup> have observed fat necrosis of the breast, and Parsons<sup>45</sup> has shown that it may occur in any fatty tissue following an injury. Fabyan<sup>46</sup> described fat necrosis of the subcutaneous tissue

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39. Eggers, E. C.: *Ann. Surg.* **80**:193 (Aug.) 1924.

40. Senn, N.: *The Surgery of the Pancreas*, *Am. J. M. Sc.* **92**:143, 1886; **93**:121, 1887.

41. Flexner: *J. Exper. Med.* **8**:167, 1906.

42. Levin: *J. M. Research* **16**:419, 1907.

43. Primrose, A.: *Surg., Gynec. & Obst.* **34**:431 (April) 1922.

44. Lee, B. S., and Adair, F. E.: *Traumatic Fat Necrosis of the Female Breast and Its Differentiation from Carcinoma*, *Ann. Surg.* **80**:67 (Nov.) 1924.

45. Parsons, W. B., Jr.: *Traumatic Fat Necrosis*, *J. A. M. A.* **83**:1756 (Nov. 29) 1924.

46. Fabyan, quoted by Opie (footnote 7).

of the face in a 14 day old infant. Farr <sup>47</sup> produced subcutaneous fat necrosis, and expressed the opinion that it is due to a simple ischemia or liberation of lipase by the fat cells. Gottesman and Zemansky <sup>48</sup> expressed the belief that it may result from decomposition of the duct contents in the breast.

Bile has been known for years to be a factor in the production of acute pancreatitis, although its particular action has not been determined. Bradley and Taylor <sup>49</sup> have demonstrated, experimentally, that autolysis does not parallel the rapid chemical cytolysis of various parenchymatous tissues immersed in bile or its salts. They found that bile did not activate the enzymes associated with autolysis or act as a coferment, and concluded that the action must be chemical. Others have shown that bile markedly accelerates the action of the pancreatic enzymes.

Bunting and Brown <sup>50</sup> found that measured small amounts of bile introduced into contact with the pancreas resulted in acute hemorrhagic changes and death. Brocq and Morel <sup>51</sup> have shown that in order to produce an acute pancreatitis with small amounts of normal bile injected into the pancreatic duct, the injection must be made about three hours after a meal, during the height of secretion. Opie <sup>52</sup> found that it was necessary to inject considerable amounts of bile, which introduces the factor of trauma. Nordmann <sup>53</sup> found that bile alone rarely produced small areas of necrosis, but that when infection was also introduced, acute pancreatitis resulted.

Tatum found that whole bile was more toxic on parenchymatous organs, although less penetrating than the bile salts, which, also, were more toxic than the acids. Archibald found that solutions of both sodium glycocholate and sodium taurocholate, in the strength normal in human bile, produced a mild form of acute necrosis of the pancreas in cats following injection into the gallbladder. Flexner obtained necrosis by injecting bile salts, especially the taurocholate, into the pancreatic ducts.

Brocq and Binet <sup>54</sup> injected sodium taurocholate into the pancreatic duct, with a negative result, but obtained an acute pancreatitis with

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47. Farr, C. E.: Ischemic Fat Necrosis, *Ann. Surg.* **77**:513, 1923.

48. Gottesman and Zemansky: Fat Necrosis of the Breast, *Ann. Surg.* **85**:438 (March) 1927.

49. Bradley and Taylor: *J. Biol. Chem.* **29**:281, 1917.

50. Bunting and Brown: The Pathology of Intraperitoneal Bile Injections in the Rabbit, *J. Exper. Med.* **14**:445, 1911.

51. Brocq and Morel, quoted by Brocq, footnote 3.

52. Opie, E. L.: *Diseases of the Pancreas*, Philadelphia, J. B. Lippincott, 1910; *Bull. Johns Hopkins Hosp.* **12**:182, 1901.

53. Nordmann, O.: *Arch. f. klin. Chir.* **127**:600, 1923.

54. Brocq, P., and Binet, L.: *Pathogénie de la pancréatite hémorragique*, *Presse méd.* **31**:219 (March 7) 1923.

sodium glycocholate. They obtained no effect with biliverdine. Archibald found that sterilized mucin-free bile produced a mild pancreatitis similar to that obtained after injecting the bile salts into the gallbladder, while the injection of infected ox bile almost regularly produced a fatal pancreatitis. This infected bile showed an increased sodium taurocholate. Archibald demonstrated areas of focal necrosis in the liver within twenty minutes after the production of experimental pancreatitis. Clinically, Fischler<sup>55</sup> found areas of focal necrosis in the liver.

Archibald believed that there were three factors involved in acute pancreatitis: a change in the composition of the bile, an undue resistance, perhaps spasm, of the common duct sphincter and an abnormal rise of pressure in the gallbladder or the bile ducts, producing a reflux of bile into the pancreas. Bile may enter the pancreatic ducts, clinically, by two methods: (1) by obstruction of the common outlet in cases in which the bile and pancreatic ducts join, and (2) by regurgitation of the duodenal contents.

In the human being, the anatomic relation of the common bile duct and the pancreatic duct through which obstruction of the outlet may divert bile into the pancreatic duct, or vice versa, is of great importance. Opie was the first to emphasize the occurrence of acute pancreatitis by means of a gallstone obstructing the ampulla beyond the junction of these two ducts. Since then, the association of gallstones, especially in the gallbladder, has been observed frequently. Egdahl<sup>56</sup> found them in 42 per cent of 105 cases of acute pancreatitis. The normal incidence of gallstones in persons between 21 and 60 years of age, as noted by Mosher<sup>57</sup> in necropsy statistics, is 8.9 per cent.

Zuckerlandl<sup>58</sup> and other anatomists have found that the accessory pancreatic duct usually communicates with the major pancreatic duct by a wide opening, but that near its entrance into the duodenum the accessory duct is reduced in size and is occasionally obliterated.

Opie found in dissections in one hundred cases that the two pancreatic ducts were anastomosed in 90 per cent. The duct of Wirsung was larger in eighty-four, and the duct of Santorini in six instances. In the eighty-four cases in which the duct of Wirsung was larger, the duct of Santorini was obliterated in twenty-one. In the six cases in which the duct of Santorini was larger, both ducts were patent, while in the ten cases in which the two ducts did not anastomose, the duct of Wirsung was larger in five instances and the duct of Santorini in five.

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55. Fischler: *Deutsches Arch. f. klin. Med.* **100**:338, 1910.

56. Egdahl: *J. Exper. Med.* **9**:385, 1907; *Bull. Johns Hopkins Hosp.* **18**:130, 1907.

57. Mosher: *Bull. Johns Hopkins Hosp.* **12**:253, 1901.

58. Zuckerlandl, quoted by Oser (footnote 25).



From measurements of the ampulla at the junction of the bile and pancreatic ducts, Opie believed that it was possible for a gallstone to produce a reflux of bile in 30 per cent of the cases.

Baldwin,<sup>59</sup> in a study of ninety cases, found that the ducts opened separately into the duodenum in 25.8 per cent, while in 74.2 per cent, there was a common ampulla. Mann and Giordano<sup>60</sup> believed from their observations that the reflux of bile was anatomically possible in only 4.5 per cent. Cameron and Noble<sup>61</sup> were able to impact a carefully selected calculus in the ampulla of Vater, and to produce a reflux of fluid from the bile ducts into the pancreatic duct in 65 per cent of one hundred cases.

Obstruction at the ampulla in the absence of gallstones may be due to a spasm of the sphincter of Oddi (Archibald), congestion, inflammatory swelling, and obstruction by mucus and by intestinal parasites. The resistance of the common duct sphincter varies considerably in animals and also in the human being, as evidenced by a difference in tension of the gallbladder at operation. Archibald<sup>62</sup> found the resistance of the sphincter to be from 500 to 650 mm. of water in animals, while Mann<sup>63</sup> rarely found it over from 100 to 150 mm. I<sup>64</sup> observed it to average from 100 to 250 mm., although there was considerable variation beyond these limits. The resistance may be temporarily and partially reduced by the application of a 25 per cent solution of magnesium sulphate. Archibald produced a spasm of the sphincter by the introduction of a 3 to 5 per cent solution of hydrochloric acid into the duodenum, followed by acute pancreatitis, although this usually required a slightly increased pressure in the biliary system.

In a human pancreatic fistula, Villaret and Justin-Besancon<sup>65</sup> found that magnesium sulphate in the jejunum produced the appearance of bile without pancreatic secretion, while hydrochloric acid produced the opposite effect. Local duodenal congestion and catarrhal inflammation of the papilla may cause stasis and reflux of bile into the pancreas.

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59. Baldwin: The Pancreatic Ducts in Man Together with a Study of the Microscopical Structure of the Minor Duodenal Papilla, *Anat. Rec.* **5**:197, 1911.

60. Mann, F. C., and Giordano, A. S.: Bile Factor in Pancreatitis, *Arch. Surg.* **6**:1 (Jan.) 1923.

61. Cameron, A. L., and Noble, J. F.: Reflux of Bile up the Duct of Wirsung Caused by an Impacted Biliary Calculus, *J. A. M. A.* **82**:1410 (May 3) 1924.

62. Archibald, E.: A General Consideration of Pancreatitis, *Internat. Clin.* **2**:1, 1918.

63. Mann, F. C.: A Study of the Tonicity of the Sphincter at the Duodenal End of the Common Bile Duct, *J. Lab. & Clin. Med.* **5**:106, 1919.

64. McWhorter, G. L.: The Surgical Significance of the Common Duct Sphincter, *Surg., Gynec. & Obst.* **32**:124 (Feb.) 1921.

65. Villaret and Justin-Besancon: *Arch. d. mal. de l'app. digestif* **15**:751 (Oct.) 1925.

Balo and Ballon<sup>66</sup> reported three cases of acute pancreatitis with obstruction of the papilla due to venous congestion resulting from a decompensated heart; others have noted these findings due to gastroduodenitis, following dietary indiscretion or accompanying catarrhal jaundice.

That a reflux of pancreatic juice may occur into the biliary tract is evidenced by the finding of trypsin in sterile bile in a case of gangrenous cholecystitis by Schonbauer.<sup>67</sup> Experimentally, he was able to produce a gangrenous cholecystitis with trypsin in sterile bile together with obstruction of the outlet. This occurrence has been corroborated experimentally by the recent work of Wolfer.<sup>68</sup>

The presence of the almost constant anastomosis observed between the two pancreatic ducts in the presence of patency of both ducts and the junction of the major duct with the bile duct above the sphincter would seem to predispose to a reflux of bile into the pancreas. Under these conditions, increased biliary pressure would tend to produce a reflux of bile into the pancreas regardless of the amount of pancreatic secretion due to the release of pressure by way of the accessory duct. In the absence of this anastomosis between the two pancreatic ducts and in the presence of obstruction at the ampulla during the height of pancreatic secretion, it is possible that pancreatic juice might be regurgitated up the biliary ducts and into the gallbladder.

It has been observed after cholecystectomy that either the bile ducts may dilate with a continent sphincter at the outlet (Rost<sup>68</sup>), or the sphincter of Oddi may dilate with incontinence (Judd). There may be a disturbed nerve reflex leading to relaxation of the common duct sphincter, as previously suggested (McWhorter, 1921) and recently favored by Puestow<sup>69</sup> because of his observing a rapid loss of sphincter tonus after cholecystectomy. Unless such a reflex loss of sphincter tone occurs after cholecystectomy, there must occur an initial increased biliary pressure until either the bile ducts dilate to compensate for the gallbladder or the common duct sphincter becomes dilated and incontinent.

A primary increased biliary pressure occurring after a cholecystectomy would seem to predispose to an acute pancreatitis. In chronic pancreatitis, Judd believes that cholecystectomy is curative, while Archibald advocates prolonged common duct drainage. Acute pancreatitis with cyst formation occurred after cholecystectomy in a case of Ballin and Saltzstein.<sup>70</sup> However, one patient (Miller<sup>1</sup>) died of

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66. Balo, J., and Ballon, H. C.: Effects of Retention of Pancreatic Secretion, *Surg., Gynec. & Obst.* **48**:1 (Jan.) 1929.

67. Schonbauer: *Arch. f. klin. Chir.* **130**:427 (Aug. 29) 1924.

68. Rost: *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **26**:711, 1913.

69. Puestow, C. B.: *Proc. Staff Meet., Mayo Clin.* **6**:23 (Jan. 14) 1931.

70. Ballin, M., and Saltzstein, H. C.: Pancreatic Cyst Following Cholecystectomy, *J. A. M. A.* **76**:1484 (May 21) 1921.

acute pancreatitis a few days after drainage of the gallbladder was performed with removal of stones, although no changes were noted in the pancreas at the time of operation.

Acute pancreatitis with death resulted from the reflux of bile into the pancreatic duct owing to the swelling of the papilla from instrumental dilatation at operation in a case of Rost.<sup>71</sup> He formerly dilated the papilla of Vater and sutured the common duct after a choledochotomy.

Regurgitation of duodenal contents into the pancreatic ducts, with or without infection, may produce necrosis of the pancreas. Experimentally, Polya<sup>72</sup> produced typical pancreatitis by injections of small amounts of duodenal contents. There are a number of factors in the duodenum that may produce pancreatitis, including bile, gastric juice, enterokinase, intestinal secretions and bacteria.

In support of the duodenal origin of acute pancreatitis may be mentioned the large proportion of clinical cases in which the bile tract was not inflamed, although the condition of the sphincter was not often determined. The actual method of duodenal origin has rarely been demonstrated clinically. Opie and Barling have been unable to force duodenal contents into the bile or pancreatic ducts in human specimens. It is possible that a regurgitation might occur into the pancreatic duct in the presence of an acute or chronic (Leveuf<sup>73</sup>) dilatation of the duodenum or with a relaxed or dilated sphincter. This may be favored by antiperistalsis (Hlava).

Intestinal parasites may carry toxic products or infection into the pancreatic ducts and obstruct them, producing acute pancreatitis (Rigby<sup>74</sup> and Novis<sup>75</sup>). Carnot produced acute pancreatitis by passing a thread into the pancreatic duct and irritating the duodenum with croton oil. Hess<sup>76</sup> produced it by fastening a funnel-shaped cannula in the duct and obstructing the duodenum below it. He believed that olive oil in the duodenum favored the production of pancreatitis. Brocq produced the condition experimentally by complete obstruction of the duodenum following a gastro-enterostomy. Seidel<sup>77</sup> also produced pancreatitis by stasis of the duodenum.

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71. Rost: *Zentralbl. f. Chir.* **54**:20 (Jan. 1) 1927.

72. Polya: *Berl. klin. Wchnschr.* **43**:1562, 1921.

73. Leveuf, J.: *Rev. de chir., Paris* **58**:616, 1920; quoted by Brocq (footnote 3).

74. Rigby, H. M.: *Acute Hemorrhagic Pancreatitis: Round Worms in Pancreatic Duct*, *Brit. J. Surg.* **10**:421, 1923.

75. Novis: *Partial Obstruction of the Pancreatic Duct by Round Worms*, *Brit. J. Surg.* **10**:421, 1923.

76. Hess: *München. med. Wchnschr.* **52**:644, 1905.

77. Seidel, quoted by Brocq (footnote 3).

Clinical cases have been observed by Gerhardi<sup>78</sup> and Konig-Werth<sup>79</sup> with stenosis of the duodenum. The duodenal origin of pancreatitis seems probable in a number of instances in which the common bile and pancreatic ducts were found to empty separately (Opie and Barling). Johnstone<sup>80</sup> alone reported four cases. In some, necrosis was limited to the region drained by one pancreatic duct. Bassett<sup>81</sup> reported a case with necrosis limited to the region of the duct of Santorini, in which the outlet terminated in an inflamed diverticulum. There was a mucous plug in the ampulla below the junction of the bile and major pancreatic ducts, with a free communication between the two pancreatic ducts.

Opie suggested that while the delicate valves in the diverticulum of Vater may normally prevent regurgitation, in 10 per cent of the cases the duct of Santorini is the chief outlet, and its orifices may be less able to prevent regurgitation. He reported such a case with complete necrosis along the unusually large duct of Santorini, the orifice of which admitted a probe 2 mm. in diameter, but there were only slight changes along the small duct of Wirsung.

Brocq expressed the belief that the greater predominance of hemorrhage in some cases of acute pancreatitis and of fat necrosis in others is due to a different origin. In the former, it was due to the duodenal contents, with a particularly increased trypsin activity and digestion of the blood vessel walls, while in the latter it was due to bile, with a resulting increased action of the lipase on the fats.

Acute pancreatitis may be produced by the injection of diphtheria toxin (Carnot and Brocq), acid gastric juice (Hlava), alkalis (Flexner), calcium chloride, formaldehyde and leukocytes without bacteria, although normal serum injected into the duct under strong pressure did not produce it (Brocq). In the absence of a chemically toxic bile in the pancreas, the production of a cytokinase or the activation of trypsin may be obtained in some other way. That diastase and other ferments are usually present in acute pancreatitis is evidenced by their early, frequent occurrence in increased amount in the blood and urine and their absence in other abdominal conditions (Unger and Heuss<sup>82</sup>).

Trauma from increased pressure in the pancreatic ducts may be of considerable importance in acute pancreatitis. Degenerative changes, such as atheroma of the blood vessels, resulting in spontaneous hemorrhage, those associated with tumors and cysts and those resulting from the toxins of bacteria and infectious diseases may produce pancreatitis. A combination of two or more predisposing factors may be necessary to produce acute pancreatitis in many instances.

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78. Gerhardi, quoted by Hess (footnote 76).

79. Konig-Werth, quoted by Hess (footnote 76).

80. Johnstone: *Colorado Med.* **4**:93, 1907.

81. Bassett: *Tr. Chicago Path. Soc.* **7**:83, 1907.

82. Unger and Heuss: *Zentralbl. f. Chir.* **54**:769 (March 26) 1927.

Fat necrosis is a frequent but not necessary occurrence in acute pancreatitis (Balser<sup>83</sup>), and Ponfick<sup>84</sup> early directed attention to fat necrosis in the fat of the omentum and peritoneum. Moynihan observed fat necrosis in the fat of the abdominal wall in acute pancreatitis. Fitz has shown that fat necrosis is rare in the suppurative type. Fat necrosis is often widely disseminated, and has been seen in the pericardium. Oser believed that these changes are not a result of contact with pancreatic secretion. However, in experimental pancreatitis, fat necrosis has been found just as widespread by Opie. Wells<sup>85</sup> has suggested the rôle of the lymphatics in this diffusion. Local congestion and the extravasation of ferments from the blood might be considered as a possible source. Several cases of fat necrosis without gross lesions of the pancreas are reported. Opie expressed the belief that some of these were due to obstruction of the pancreatic duct by a gallstone. Wood<sup>86</sup> suggested that the fat-splitting ferment, steapsinogen, may be activated in the pancreas by some constituent of the bile. Flexner demonstrated a fat-splitting enzyme in the necrotic foci.

The pathologic changes are the result of the splitting of fat into soluble glycerin and fatty acids, which are deposited as needle-like crystals within the necrotic cells and later unite with calcium, forming globular masses. The small areas of necrosis are surrounded later by a zone of round cell infiltration. Wells found that a moderate amount of fat necrosis might be absorbed in a week after its production. He found that pancreatin injected into the peritoneal cavity produced fat necrosis.

While experimental section of the pancreatic duct does not produce acute pancreatitis, I have observed in one instance several widely scattered areas of fat necrosis on the pancreas. Flexner showed that sterile but activated pancreatic juice may cause pancreatitis. Activation of trypsin is believed to result from some substance formed in the autolyzed pancreas (Lattes<sup>87</sup>). Wells observed that trypsin and lipase were inactive after autolysis, although trypsin was still present.

Fitz found that autolysis destroyed the fat ferment but not the tryptic ferment, which may explain the absence of fat necrosis in extensive necrotic pancreatitis. Injury to the pancreas may produce a cytokinase, and there may also be a leukokinase and a bacteriokinase (Brocq and Binet). Rewbridge has shown that bile free in the

83. Balser: Ueber Fettnekrose, Virchows Arch. f. path. Anat. **90**:520, 1882.

84. Ponfick: Virchows Arch. f. path. Anat. **56**:541, 1872.

85. Wells, H. G.: J. M. Research **9**:70, 1903; Chemical Pathology, Philadelphia, W. B. Saunders Company.

86. Wood, W. Quarry: The Etiology of Acute Pancreatitis, Edinburgh M. J. **30**:201 (May) 1923.

87. Lattes: Pathologica **4**:577, 1912, quoted by Goodpasture and Clark: Bull. Johns Hopkins Hosp. **18**:2, 1919.

peritoneal cavity may produce fat necrosis, and that this is due to the action of the bile salts. He suggested that the pancreatic enzymes are liberated by permeability changes produced by the local action of the bile on the pancreas.

There are several theories regarding the cause of death in acute pancreatitis in which the following conditions are considered: nervous shock, anaphylaxis, toxemia and local or generalized infection.

The theory that a nervous shock is produced is based on the adjacent sympathetic plexus. Linder<sup>88</sup> believed that early acute prostration may result from pressure of an enlarged pancreas against the celiac plexus, and that later a toxemia occurs. Archibald and Kaufman<sup>89</sup> believed that irritation of the plexus may produce paralysis of the intestine with neurogenic shock. The resemblance to an anaphylactic shock is advocated by Silvestri,<sup>90</sup> who suggested that sensitization is produced by previous mild attacks of pancreatitis. Toxemia undoubtedly may develop rapidly from local infection in the pancreas or peritoneum.

Toxemia is usually believed to be due to the split products of pancreatic autolysis (Guleke<sup>91</sup>) or digestion by trypsin (Whipple and Goodpasture<sup>92</sup> and Tower). This toxemia is evidenced by an increased proteose index, and is not due directly to an increase in trypsin in the blood, although an increase in anti ferment favors recovery (Peterson, Jobling and Eggstein<sup>93</sup>).

Goodpasture and Clark<sup>94</sup> have found a toxic constituent that may be gradually destroyed by autolysis in fresh pancreas, before activation of trypsinogen. However, if trypsinogen is activated by the duodenal juices, immediate death may result, as observed by Lombroso<sup>95</sup> and Roger and Garnier.<sup>96</sup> Archibald and Kaufman explained the belief that the particular toxin in acute pancreatitis was probably a histamine. The peritoneal exudate was formerly considered toxic (Guleke); however, Cook and Whipple<sup>97</sup> and Whipple and Goodpasture injected this

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88. Linder, W.: *Acute Pancreatitis*, J. A. M. A. **69**:718 (Sept. 1) 1917.

89. Archibald, E. A., and Kaufman, M., in Lewis, Dean: *Practice of Surgery*, Hagerstown, Md., W. F. Prior Company, Inc., 1929.

90. Silvestri, T.: 1922, quoted by Brocq (footnote 3).

91. Guleke, N.: *Beitr. z. klin. Chir.* **48**:127, 1906. Gross, O., and Guleke, N.: *Die Erkrankungen der Melz der Leber, der Gallenwege und des Pankreas*, Enzyklopaedie der klinischen Medizen, Berlin, Julius Springer, 1924, p. 115.

92. Whipple and Goodpasture: *Surg., Gynec. & Obst.* **17**:541 (Nov.) 1913.

93. Peterson, Jobling and Eggstein: *J. Exper. Med.* **23**:491, 1916.

94. Goodpasture and Clark: *A Study of a Toxic Substance of the Pancreas*, *Bull. Johns Hopkins Hosp.* **18**:2, 1919.

95. Lombroso, quoted by Wood (footnote 86).

96. Roger and Garnier: *Compt. rend. Soc. de biol.* **64**:885, 1908.

97. Cook and Whipple: *J. Exper. Med.* **28**:223 (Aug.) 1918.

fluid into the peritoneum and veins of animals without any ill effects. They concluded that the toxemia was nonspecific and resulted from the breaking up of protein and cell autolysis. Egdahl found that autolyzed pancreatic extracts depressed blood pressure, and that the toxic effects were greatest when the protein had been completely digested.

Sweet,<sup>98</sup> Doberauer<sup>99</sup> and Guleke removed a part of the pancreas aseptically from one animal and placed it in the peritoneal cavity of another; death invariably occurred in twenty-four hours. However, bacteria may be present in the normal pancreas of animals (L. Dragstedt).

Whipple<sup>100</sup> has called attention to a postoperative asthenia due to acute and chronic lesions of the pancreas, followed by a high mortality.

Fat necrosis is probably not the toxic factor in acute pancreatitis, since it may occur alone without toxic general symptoms, and it is frequently more extensive in the older and less toxic cases.

The following study is based on an analysis of sixty-four cases of acute idiopathic pancreatitis.

#### ETIOLOGY AND PREDISPOSING FACTORS

The age in all sixty-four cases varied from 19 to 70 years, but was chiefly between 30 and 60 years. The average age was 43.3 years. Comparing the average ages in the four pathologic types or grades of pancreatitis, the youngest age, 39 years, occurred in the highly fatal hemorrhagic type II; the next higher age, 42 years, occurred in the subacute type I; the age in the suppurative type IV averaged 47 years, and the highest average age, 51 years, was in the gangrenous type III. This comparison shows the mortality rates to be higher in the youngest, the hemorrhagic type, and in the oldest, the gangrenous type, than in the others (table 1).

There were an equal number of both men and women, which is at variance with the reports of most authors that acute pancreatitis is much more frequent in men.

In comparing the sex incidence in the different pathologic types of pancreatitis, it was found that almost an equal number of each sex had the subacute and the hemorrhagic types. More women than men had the gangrenous type, but nine men and three women had the suppurative type. This tends to confirm the theory that infection is more commonly associated with pancreatitis in the male.

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98. Sweet: *Internat. Clin.* 4:293, 1915.

99. Doberauer: *Beitr. z. klin. Chir.* 48:127, 1906.

100. Whipple, A. O.: Pancreatic Asthenia as a Postoperative Complication in Patients with Lesions of the Pancreas, *Ann. Surg.* 78:176 (Aug.) 1924.

Among the twenty-six patients having gallstones, there were eleven men, with six deaths, a mortality of 54 per cent, and fifteen women, with eight deaths, a mortality of 53 per cent. However, gallstones occurred in only 30 per cent of the men who died, as compared to an occurrence of 53 per cent in the women who died. Considering the

TABLE 1.—*Etiology, Predisposing Factors and Treatment in Pancreatitis*

	Number of Cases	Percentage of Frequency of Mortality	Percentage of Mortality
Idiopathic acute pancreatitis.....	64	..	54.7
Type I, acute edematous pancreatitis.....	18	28	28
Type II, acute hemorrhagic pancreatitis.....	27	42	70
Type III, acute necrotic or gangrenous pancreatitis.....	7	10	70
Type IV, acute suppurative pancreatitis.....	12	20	50
Men in total of 64 cases.....	32	50	62
Women in total of 64 cases.....	32	50	47
Obesity in total of 64 cases.....	17	26	85
Alcoholism in total of 64 cases.....	7	11	70
History of typhoid fever.....	5	8	60
Numerous childbirths .....	7	11	42
Emaciation .....	5	8	64
Jaundice .....	9	14	55
No previous abdominal symptoms.....	17	26	50
Sugar in the urine.....	8	12	62
Some type of diseased gallbladder, total.....	35	54.5	52
Gallstones, total .....	26	40	53
Gallstones in 32 men .....	11	34	54
Gallstones in 32 women .....	15	47	53
Acutely inflamed gallbladder.....	14	22	50
Gallstones with chronic inflammation but without acute gallbladder changes .....	18	28	55
Chronic inflamed gallbladder without stones.....	3	5	33
Acutely inflamed gallbladder without stones.....	6	9	50
Gallstones with acute inflammation of the gallbladder...	8	12	50
Chronic inflammation of the gallbladder, with and with- out stones, total.....	21	33	57
No acute or chronic gallbladder inflammation, total.....	29	45	58.8
(a) Gallbladder distended .....	8	12	37
(b) Gallbladder noted as definitely normal.....	16	25	56
(c) Gallbladder not mentioned .....	4	6	50
Treatment:			
(a) No operation .....	6	9	100
(b) Operation; exploration without drainage.....	7	11	57
(c) Operation with four chief types of drainage.....	51	80	49
1. Drainage only of peritoneal cavity.....	13	20	77
2. Drainage of pancreas alone, with and without abscess .....	4	6	None
3. Drainage of gallbladder or common duct....	25	39	56
4. Drainage of gallbladder and pancreas.....	9	14	11

much higher mortality rate in men (62 per cent) than in women (47 per cent), this observation would indicate that other factors than gallstones may cause and influence the mortality in acute pancreatitis.

Although gangrenous pancreatitis developed more commonly in women and the suppurative type more commonly in men, the mortality was lower in the latter type, so that suppuration was probably not the chief factor in increasing the mortality. It is probable that non-suppurative and anaerobic infection were present in some of the other cases, especially in the gangrenous group.



The mortality rates in the cases with acute inflammation of the gallbladder but without stones were practically equal in both sexes, but the series was small.

*Childbirth.*—In two patients, the onset of pancreatitis occurred shortly after childbirth, four days in Percy's patient and three weeks in Gatewood's. In the latter, there had been previous frequent attacks, with acute cholecystitis also found at operation. In both instances, there were gallstones, and both patients recovered. Seven patients had borne numerous children, but some records were incomplete.

There was a history of typhoid fever in five cases (three women and two men). Two of these patients had type I pancreatitis, two had type III and one had type II. Other previous diseases noted were: arthritis deformans, twice; pneumonia, once; malaria, once; pyorrhea and otitis media, once, and syphilis, once. Several patients had been operated on previously—appendectomy, twice; gallstones with removal of the gallbladder and drainage, once; a pelvic operation, once; an abdominal abscess, once, and a perforated duodenal ulcer two weeks previous to the attack, once.

There were seventeen, or 26 per cent of the patients, who were definitely obese and five who were emaciated. Practically all of the remaining patients were stated to be well nourished. The cases of suppurative pancreatitis, type IV, showed the greatest number of obese patients and the cases of gangrenous pancreatitis, type III, the fewest.

There were seven patients, or 11 per cent, who gave a history of persistent alcoholism. A few others were occasional drinkers. The alcoholic patients nearly all had hemorrhagic pancreatitis, type II. In two instances the onset occurred the morning after a drinking bout.

*Exciting Factors.*—Infection in the pancreas or its surroundings was noted in a number of instances, but few bacteriologic studies were recorded. The rare occurrence of acute or chronic inflammation, except in the biliary tract and the pancreas, in both the cases that came to necropsy and those in which operation was performed, suggests an interrelation of their infection. Acute inflammation of the gallbladder was described in fourteen, or 22 per cent, of the sixty-four cases. Gallstones were found with chronic inflammation in eighteen, or 28 per cent, and chronic inflammation without stones in three cases, or 5 per cent. There was a total of some type of acute or chronic inflammation or stones in the gallbladder in thirty-five cases, or 55 per cent of the total.

Seventeen of the twenty-nine patients in whom the gallbladder was considered to have no acute or chronic inflammation gave a history of previous symptoms in the upper part of the abdomen. However, one had a duodenal ulcer.

No symptoms or evidence of any foci of infection was noted as a source of the acute pancreatitis in these cases, and practically all patients were in excellent health at the onset. Since sixteen had previous symptoms in the epigastrium without any other pathologic process than pancreatitis, it is possible that they suffered from mild attacks of pancreatitis, although attacks of cholecystitis may have occurred leaving no gross changes. If these previous symptoms were due to attacks of pancreatitis, they were probably limited to the pancreas and due to local conditions, such as diversion of bile, extension of infection along the lymphatics, bile ducts or blood vessels, or the activation of latent infection.

In eleven other cases in which the patients had a normal gallbladder and had had no previous symptoms, infection from the biliary tract seems unlikely as a cause for the acute pancreatitis. The presence of acute inflammation of the gallbladder in only 22 per cent of the entire series also speaks for this as a secondary condition. The diversion of bile into the pancreatic ducts may produce acute pancreatitis, without primary infection, although infection may subsequently develop within the gland or extend from the duodenum. In the presence of gallbladder infection one may infer that the infection spread to the pancreas or vice versa. When infection occurs in the gallbladder, it may produce chemical changes in the bile that render it toxic and may activate the pancreatic juices when regurgitated into the pancreas.

The evidence speaks against infection as the exciting factor in the first three types of pancreatitis and indicates that when infection occurred, it was a complication.

Infection may ascend the ducts in the presence of inflammatory obstruction at the ampulla or rapidly permeate the intestinal wall, following distention and stasis, especially with necrosis or gangrene of the pancreas. It is possible that hematogenous emboli may have occurred in one instance (Miller), although local infection is the more probable.

In favor of regurgitation of bile as a cause of pancreatitis is a case that came to necropsy in which the pancreatic duct was found bile-stained, and several cases in which obstruction was present at the ampulla, including two with an impacted gallstone. Obstruction may have been overlooked in other instances, or only temporary obstruction may have occurred, such as obstruction due to a stone, muscle spasm, inspissated mucus, congestion or inflammation.

In cases in which diversion of bile at the ampulla was anatomically impossible, a regurgitation of activating juices or extension of infection from the duodenum may have occurred.

## PATHOLOGY

A division of acute pancreatitis into four pathologic types seemed advisable for this detailed study. Although these types represent different degrees of severity of the process, the classification conforms to the condition found at the time of examination and represents the particular stage at that time rather than the final degree of the pathologic process. To a large extent the four types represent a varying degree of severity and rate of extension of the process. It is quite probable that different factors may predominate in the pathogenesis of each type, and certainly the diagnosis, prognosis and treatment may be more correctly determined by such a working classification.

Type I includes eighteen cases of acute or subacute pancreatitis in which no hemorrhage was seen or recorded and in which the pancreas was usually enlarged, edematous and hard. In two cases it was described as nodular and in two as soft, while in three instances it was described as simply edematous.

Type II includes twenty-seven cases in which hemorrhages were recorded as present in the pancreas in the absence of gross gangrene or suppuration. The pancreas was also usually enlarged and hard or edematous.

Type III includes seven cases with gross necrosis or gangrene of the pancreas in the absence of suppuration.

Type IV includes twelve cases in which there was suppuration or a definite abscess in the pancreas. In four cases there was also necrosis.

Microscopic examinations were made in three cases at necropsy. There was extensive necrosis in one and leukocytic infiltration in one; in the other there was no normal pancreatic tissue, only areas of degeneration separated by loose connective tissue with infiltration of small round cells. There was one case of syphilis of the liver in type III. Areas of fat necrosis were examined in five cases. They showed small areas of necrosis surrounded by an infiltrated zone of small round cells and leukocytes in the fat tissue.

There was a tumor or enlargement in the epigastrium in thirty-four cases, although it was palpated clinically in only fifteen instances. In three other cases in which a tumor was diagnosed clinically, it was not found at operation. The frequency of a mass was about the same in the various types of pancreatitis. The mass was found to be an enlarged pancreas in twenty-one cases, a thickened omentum in four, an abscess in four, a retroperitoneal hemorrhage in two, and in two (Percy-Nadeau and J. Smith) a pseudocyst with suppuration in the pancreas (McWhorter<sup>101</sup>).

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101. McWhorter, G. L.: Cysts of the Pancreas, *Arch. Surg.* **11**:619 (Oct.) 1925.

Fluid was present in the abdomen in thirty-eight cases, or 60 per cent, and it was often quite abundant. The frequency was about the same in all types, although somewhat greater in type I. The type of fluid was described as bloody fourteen times, yellow twice, greenish or bile-stained four times, chocolate-colored three times, slate-colored once, turbid twice, and containing fat globules once. Bloody fluid was more frequent in the hemorrhagic type, and bile-stained in the suppurative type. In the patients having fluid, the mortality was 66 per cent.

Fat necrosis was recorded as present in fifty-five, or 83 per cent, of the sixty-four cases. In two cases in which it was not recorded, there was suppuration.

Gallstones were the most frequent associated pathologic condition. They were found either at operation or at necropsy in twenty-six, or 40 per cent, of the patients, of whom fourteen died. Gallstones were found in the common duct in five patients. In two who died a stone was found at necropsy impacted in the ampulla of Vater. There was obstruction, with jaundice due to inflammation of the common duct, but without stones, in two other cases. In one, the common duct was distorted and narrowed.

Acute inflammation of the gallbladder was present in fourteen, or 22 per cent, of the patients, of whom seven died. There were gallstones present in eight of these, with four deaths. Chronic inflammation of the gallbladder was noted in twenty-one cases, with eleven deaths. This condition was fairly equally distributed among the four types of pancreatitis.

In twenty-five cases, or 39 per cent, in which the gallbladder was not recorded as inflamed, there were fifteen deaths, or a mortality of 60 per cent. The gallbladder was distended in eight of these, with three deaths. In sixteen, the gallbladder was recorded as perfectly normal, with nine deaths, or 56 per cent.

Thick black bile was reported in four cases, with three deaths. If four cases in which the gallbladder was not mentioned, with two deaths, are considered as showing no disease of the gallbladder, there is a total of twenty-nine cases having no evidence of involvement of the gallbladder, with a mortality of 58.8 per cent.

Among the fifteen patients examined post mortem, there was involvement of other viscera than the pancreas and the biliary tracts, including the gallbladder, in only nine. Infection was the cause of most of the associated pathologic involvement, usually due to a local extension and occasionally to pyemia. There was acute suppurative pleuritis, once; bilateral fibrous pleuritis, twice; subphrenic abscess, once; abscess of the kidney with bronchopneumonia, once, and phlegmonous gastritis with multiple embolic abscesses of the liver, once.

There was chronic perihepatitis, gastritis and splenitis with pleuritis, once; chronic interstitial hepatitis, once; syphilitic hepatitis with gummas, once, and local perforating ulceration into the colon, once. Degenerative and late changes were usually associated with infection. In the liver, fatty changes were observed in four cases. In the kidney, chronic nephritis was noted twice, cloudy swelling twice and fatty changes once. In the spleen, thrombosis of the splenic vein and hyperplasia were each noted in one case. In the heart, fatty changes were observed in one case.

Acute parotitis occurred in three patients after operation, and all died. In one, there was local pancreatic sepsis, and in another systemic sepsis for three days. Digestion of the wound was much less common than is usually believed. It occurred in three suppurative cases. In one case, the wound gaped widely owing to digestion of the sutures, and did not heal before death on the sixteenth day. In another, there was marked digestion about a fistulous opening for several weeks. In the remaining case, the digestive action was slight. Apparently, there may be considerable drainage of pancreatic juice, which at times may have little effect on the wound. This would indicate that factors which may activate the pancreatic juice and produce a necrosis are transient.

The cause of death was believed to be toxemia in twenty patients, of whom five were not operated on. The next most common cause was local sepsis, thirteen cases; two of these patients were not operated on. One patient died of pyemia and toxemia, and the remaining patient had a postoperative hemorrhage. In the first three types of pancreatitis, death from sepsis occurred in about the same proportion of the fatalities, while in the suppurative type IV, all six deaths were due to local sepsis.

#### SYMPTOMS

There was a history of previous attacks of acute abdominal pain in twenty-four cases, or 37 per cent. In at least two of these, the attacks were similar to the pains during acute pancreatitis. Previous attacks of pain of a milder but similar character were noted in four other cases. Two patients had been operated on previously for a condition diagnosed as chronic recurrent appendicitis.

Previous attacks of chronic distress in the stomach or abdomen occurred over varying periods of time and degree in fourteen cases, or 22 per cent. Types I and III pancreatitis were found more frequently in the patients having had previous chronic distress, and types II and IV in those giving a history of previous attacks of pain.

There were forty-two patients, or 65 per cent, exclusive of the two with chronic appendicitis, who gave a history of previous attacks of pain or abdominal distress. Among these were twenty-three in

whom gallstones or acute cholecystitis were found present during the attack of acute pancreatitis.

There were seventeen of the forty-two patients having previous symptoms of pain or distress in whom no gallstones or inflammation were noted either at operation or, in four of them, at necropsy. The occurrence of previous abdominal symptoms in practically 40 per cent of those with a normal gallbladder is suggestive of previous mild attacks of pancreatitis. There may be factors causing attacks of pain that could not be determined, such as a past cholecystitis, spasm or temporary obstruction of the common bile duct by a gallstone, without noticeable changes to be seen at operation.

There were ten patients who gave no history of previous attacks of pain or abdominal distress in whom either gallstones or acute inflammation of the gallbladder, or both, were found. Eight of these had gallstones.

The onset of the pancreatitis was acute, with no previous symptoms, in eight, or 30 per cent, of the twenty-six patients having gallstones, but acute cholecystitis was found in only four of these.

There was no history of previous abdominal symptoms in seventeen cases, or 26 per cent, with ten deaths, or 59 per cent. Four were cases of type I pancreatitis, with three deaths, or 75 per cent, which is significant, since the average mortality was 28 per cent in this type. Eight were cases of type II pancreatitis, with five deaths. There was one fatal type III case. There were four cases of type IV pancreatitis, with only one death. This would seem to favor the theory that previous mild attacks occur which develop immunity, and that infection is not a necessary factor, but may develop as a serious complication if the patient does not die of the toxemia.

Pain was present in all of the cases, and usually its onset was sudden, severe, prostrating and persistent. However, in one case of type IV pancreatitis, it was very slight. In two cases of a type II condition it was intermittent. In two cases of type III pancreatitis it was constant, with severe exacerbations. The location of the pain was stated to be in the epigastrium in twenty-five cases, over the region of the gallbladder in ten, at the umbilicus in two and in the right lower quadrant in three cases. In one case (Phemister), the pain was located in the right groin and thigh, simulating neuritis. There was radiation of the pain to the right shoulder twice, to the left shoulder four times and to the back once.

Rigidity was usually definite but not boardlike. It varied somewhat, and in two cases it was absent on examination. The rigidity was generalized over the abdomen in thirty cases, localized to the epigastrium in five and to the right upper quadrant in nine.

Tenderness was usually a leading complaint, and was not absent in any case. It was general in twelve, localized in the epigastrium in twelve and in the right upper quadrant in twelve cases. The locality was not stated in eleven cases.

Vomiting was usually persistent. In one instance, the vomitus was bloody. This symptom was absent in six patients and occurred only at the onset in two others. In three of the six patients in whom vomiting was absent, there was no nausea. Belching was an occasional symptom.

Fever was frequently absent or only slight during the early course. Chills were not noted. There were nine patients (14 per cent) with no recorded fever at any time before operation. Three of these had a subnormal temperature. There were four whose temperatures did not rise over 100 F. The maximum temperature in thirty cases in which it was recorded before operation averaged 102 F. The temperature varied from an average of 98 to 102 F., and often remained normal a large part of the day. Only three patients had a temperature over 103 F., and two of these had a temperature of 105 F.

The average maximum pulse rate recorded before operation in forty-two patients was 110. In two instances, the maximum pulse rate was 60 before operation; in twenty-three instances, it was over 120. In only nine patients was the rate under 100.

A bluish discoloration of the upper abdominal wall, followed later by edema, was given considerable diagnostic significance by Kanavel, and was noted in two patients.

A mass in the epigastrium was noted clinically in eighteen patients, but in three none was found at operation. There were nine in whom no tumor was palpated, and yet a definite mass was found at operation. In some instances, the inability to palpate a fairly large swelling was due to marked tympanites, which was especially frequent in the critically ill hemorrhagic type. In five other cases, an indefinite resistance was felt in the epigastrium, but no mass was found at operation.

Jaundice was observed in nine patients with five deaths. Two patients had pancreatitis type I; two, type II; two, type III, and three, type IV. There were two patients without jaundice in whose urine bile was present, and both recovered.

The urine contained sugar in eight cases, with five deaths. Albumin and casts were recorded in eighteen cases, with nine deaths. Blood was present in three fatal cases of type II. The urine was recorded as normal in ten cases, with five deaths.

The white blood count recorded in thirty-five cases averaged 20,000. Thirteen of the patients recovered with an average count of 17,000, while twenty-two who died had an average of 21,000 leukocytes. In type I, nine patients, most of whom recovered, averaged 17,000 leuko-

cytes. In type II, fourteen patients averaged 21,000, of whom eleven died. The highest count was 42,000 in a fatal case, while one patient with a count of 32,000 recovered. There were two fatal type II cases, with a count of 7,800 and 11,900, and four fatal type III cases, with an average count of 16,700. There were eight type IV cases, with an average count of 23,800, with five deaths.

The stools in one case were grayish white, containing bile but no blood. In another case, in which the patient recovered, blood was present. The bacteriologic reports in two cases (Schrager) showed a colon bacillus cultured from the gallbladder contents. In one (Percy-Nadeau) the discharge from the wound was sterile. In another (McWhorter) cultures from the very thick gallbladder bile of a critically ill patient were sterile.

Roentgenograms of the stomach in one case were negative, except for a slight six hour residue.

#### PROGNOSIS

There were thirty-five deaths in the sixty-four cases, or 54 per cent. In comparing the ages of the patients in the different pathologic types of pancreatitis it was found that the youngest average occurred in hemorrhagic type II, and the oldest in gangrenous type III. The mortality rate was the same in both, but it was higher than in the two other types. Apparently, age is not a decisive factor in the prognosis. Twenty, or 62 per cent, of the men died, and only fifteen, or 47 per cent, of the women died.

Among patients with predisposing factors, the highest mortality rate, or 85 per cent, was that of obese patients, while 90 per cent was the rate for patients with a history of alcoholism. There was a mortality of 64 per cent of those who were emaciated, and 60 per cent of those with a history of typhoid fever. For the patients who gave no history of any previous abdominal symptoms or of any serious systemic diseases, the mortality rate was 5 per cent above the average. Among the nine patients who were jaundiced, the mortality rate was 55 per cent. The development of jaundice was apparently not an especially unfavorable symptom, except in the suppurative type of pancreatitis, in which it was very serious. There was a lowered mortality, 42 per cent, among seven patients who had borne several children.

The mortality rates in cases complicated by obesity, alcoholism, previous typhoid or numerous pregnancies were compared for the different types of pancreatitis. In subacute type I, the mortality rates in all these cases, except those complicated by obesity, were lower than the average. In the hemorrhagic and gangrenous types, the mortality rate was much higher when any of the complicating factors was present, while in the suppurative type of pancreatitis, the mortality rates dropped



to below the average. The mortality curve for all cases in which any of these factors was present tends to parallel the average mortality in all types, but it was higher in the hemorrhagic and gangrenous types of pancreatitis.

The patients who recovered usually had a slightly lower average white blood count, although there were exceptions, two patients who died, with a normal count. The mortality of the eight cases in which sugar was present in the urine was 62 per cent. There were three cases of pancreatitis, type I, in which sugar was present, with one death. In the hemorrhagic type of pancreatitis, sugar was found in four cases, but in one it was present only after operation. Three of these were fatal cases. The remaining case occurred in the suppurative type and was fatal. There is apparently an increased mortality in cases of pancreatitis in which sugar occurs in the urine except in the milder cases. Diabetes developed in one patient three years later, although sugar was not found during the pancreatitis. A completely normal urine was apparently of little value in prognosis, although albumin and casts usually were present in the more severe cases. Among several hundred diabetic patients, Dunn<sup>102</sup> noted only two having a history of acute pancreatitis.

The mortality rate was studied in relation to the duration of time of the pancreatitis from the onset to the time of operation. Twenty-three patients with a recent acute onset underwent emergency operations, although the actual duration of the disease was not recorded. Nine died and fourteen recovered, but only one case had a type I pancreatitis. Eight patients were operated on less than one day from the onset of the disease. Six of these died; five had the hemorrhagic type of pancreatitis. Considering the thirty-one cases as of recent onset before operation, the mortality rate was 48 per cent, slightly less than the average.

There were fourteen cases in which over one day and less than one week had elapsed before operation, the average time being from two to four days. Nine patients died, or 64 per cent. Most of these had the hemorrhagic type of pancreatitis, with a mortality of 83 per cent. There were three cases in which the onset occurred two months previous to operation, and all the patients died. Of the six patients with pancreatitis on whom operation was not performed, all died following an acute onset.

From a further study of the deaths in the different types of pancreatitis, it is evident that they were more dependent on the extent of the pathologic involvement than on the time elapsing from onset to operation.

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102. Dunn; Vatcher and Woodwork: Diabetes as a Sequel to Acute Pancreatitis, *Lancet* 1:595 (March 20) 1926.

The lowest mortality rate was in a group of nine cases in which operation was performed at about the end of two weeks after the onset of the condition, there were only two deaths, or 22 per cent. Since these nine patients were nearly all desperately sick, it seemed worth while to study their cases in detail. There was suppuration in four cases with one death, and the other three patients would undoubtedly have died if drainage had not been instituted. In three patients with hemorrhagic pancreatitis, one having jaundice died, while in the others, who recovered, an acutely inflamed gallbladder was drained. In two of these cases of type I pancreatitis exploration was done and the wound closed without drainage, with recovery. Among the seven survivors were five women and two men, while the two deaths occurred in men. Analyzing all cases, the mortality rate was found to be lower in all four types of pancreatitis following an early operation, unless the patients were moribund at the time of operation.

The average age of all survivors in the sixty-four cases was 40 years, and that of the patients who died, 34 years. The average age of the men and the women was the same. Six patients died before they could be operated on. The length of time after operation until death occurred was compared in twenty-nine patients. Eleven deaths occurred within a day after the operation, and ten within from two to four days. The majority of the remaining eight deaths occurred within from two to three weeks, although, exceptionally, death occurred over a month after operation. These cases were divided fairly equally among the four types of pancreatitis; in the suppurative type, there were no deaths following the third day after operation.

In reviewing the mortality rates of the varying intervals before and after operation, and analyzing the different types of pancreatitis, it is evident that operation is urgently indicated in the presence of pancreatic suppuration or acute cholecystitis. Operation is also indicated for patients seriously sick at the end of the second week. It is only among patients with the nonsuppurative types of pancreatitis, including the hemorrhagic type, requiring operation at this time that there is a lowered mortality. One may conclude that operation is usually indicated as an emergency in all types of pancreatitis, at the end of the second week if there is no definite improvement.

In the absence of suppuration or gangrene in the pancreas, the inference might be drawn that mere drainage of the pancreatic capsule is of little value. If one could correctly diagnose the absence of infection in the pancreas or biliary tract, it might seem unnecessary to operate merely to drain the pancreas until complications developed, and then operation should be performed preferably about two weeks after the onset. However, it is evident that one should operate in all acute cases of pancreatitis, if possible, as an emergency procedure because of the

frequent presence of gallstones, acute cholecystitis, necrosis and infection or suppuration in the pancreas. Since it is only in the cases of non-suppurative pancreatitis in which operation has been performed that the mortality rate is low, one may conclude that drainage of the pancreas may prevent secondary anaerobic infection and suppurative changes or at least limit their extension.

The relation of gallbladder disease to the mortality is of considerable importance, because the presence of gallstones was the most frequently associated pathologic condition with acute pancreatitis. The mortality in cases with gallstones was slightly less than in those without them, except when the stones were impacted in the ampulla of Vater. Gallstones were present in twenty-six cases, with fourteen deaths, a mortality of 53 per cent. They occurred in the common duct five times, and in the two patients who died a stone was impacted in the ampulla of Vater. Comparison of the mortality rates in the four pathologic types of pancreatitis with gallstones (table 2) shows that they parallel the mortality rates in cases without stones; that is, the rate is higher in the hemorrhagic and gangrenous types.

Acute inflammation of the gallbladder was present with gallstones in eight cases, with four deaths, while in eighteen cases with gallstones but without acute inflammation, there were ten deaths, or 55 per cent.

Acute inflammation of the gallbladder was present in fourteen of the sixty-four cases, with seven deaths. The mortality was 50 per cent in eight cases with stones and in the six cases without them. While both gallstones and acute cholecystitis may predispose to pancreatitis, at first glance they apparently do not affect the average mortality rate. However, on comparing the mortality rates of the cases with acute cholecystitis in the different types of pancreatitis (table 2), it was found that the mortality was lower than the average in the hemorrhagic type of pancreatitis, and higher, or 100 per cent, in the gangrenous and suppurative types. The series is small, but it definitely indicates the seriousness of acute infection of the gallbladder in both gangrenous and suppurative pancreatitis.

Chronic inflammation of the gallbladder was recorded in twenty-one cases, with eleven deaths, a mortality of 57 per cent. Eighteen of these patients had gallstones, with a mortality of 55 per cent, and three did not have them, with a mortality of 33 per cent. The occurrence of these cases in the four different types of pancreatitis was about equal, although the mortality was unusually high, 88 per cent, in the hemorrhagic type.

The gallbladder was considered as practically normal in twenty-five cases, with fifteen deaths, or 60 per cent. In sixteen of these cases, the gallbladder was recorded as entirely normal, with nine deaths, or 56 per cent; although more of the cases occurred in the hemorrhagic

type, the mortality rates corresponded fairly well to the average. In all except two the course was found to have been fulminating in character and nearly all of these patients were operated on either the second or third day or death occurred rapidly after the onset. This would seem to indicate that the acute pancreatitis was primary, and that inflammation of the gallbladder more frequently developed in the less fulminating cases.

In four cases in which the gallbladder was not examined, there were two deaths. In eight cases the gallbladder was distended, with only three deaths; however, more of these cases occurred in type I pancreatitis. In comparing the mortality in all cases with acute inflammation of the gallbladder and those with a normal gallbladder, the mortality was found to be higher in the latter. The lowest average mortality rate of the four pathologic types of pancreatitis in the sixty-

TABLE 2.—*Mortality in the Four Types of Pancreatitis \**

	I Acute Edematous Pancreatitis, per Cent	II Hemorrhagic Pancreatitis, per Cent	III Necrotic or Gangrenous Pancreatitis, per Cent	IV Suppurative Pancreatitis, per Cent
Average mortality .....	28	70	70	50
Mortality in 26 cases with gallstones	20	66	66	33
Mortality in 14 cases with acute cholecystitis .....	33	37	100	100
Mortality in 16 cases with an entirely normal gallbladder .....	12	75	75	37

\* The mortality rates vary directly with the severity of the pathologic process in the pancreas and complicating conditions of the gallbladder.

four cases was 28 per cent in type I, which might be considered the best criterion by which to judge the prognosis as affected by gallbladder disease. On analyzing the cases in type I, 33 per cent of the patients with acute inflammation of the gallbladder died, 20 per cent having gallstones died, and only 12 per cent died in whom the gallbladder was normal (table 2).

In the suppurative type of pancreatitis the average mortality rate was 50 per cent, but in cases complicated by acute cholecystitis, it was 100 per cent. The mortality was also increased in the gangrenous type, complicated by inflammation of the gallbladder, but there was a lowered mortality in the hemorrhagic type. It is evident that the inflammation of the gallbladder did not develop at the onset in many fulminating cases, but when present it usually increased the mortality.

In the suppurative type of pancreatitis, the most serious complication next to cholecystitis was jaundice, which was present in three of the six patients who died. Aside from the cases in which jaundice was present, the mortality rate was almost as low as in type I. Appar-

ently with the development of a suppurative pancreatitis, one may expect a fairly low mortality rate if operation is performed and drainage instituted, unless jaundice is present.

#### DIAGNOSIS

The symptoms of pancreatitis are fairly characteristic, but resemble those of several other serious abdominal conditions. In subacute type I pancreatitis, two cases were correctly diagnosed. The diagnosis of an acutely inflamed gallbladder condition was made and found present in four other cases. Mistaken diagnoses were made as follows: appendicitis, once; carcinoma of the stomach, twice, and various other conditions, seven times. In two instances, no clinical diagnosis was made.

In the hemorrhagic type, three cases were correctly diagnosed. Wrong diagnoses were made as follows: acute cholecystitis, seven cases; a perforating gallbladder, two; a perforating gastric ulcer, six; acute appendicitis, two, and carcinoma of the pancreas, one. No diagnosis was made in six cases.

In the gangrenous type of pancreatitis a correct diagnosis was made once. An acute condition of the gallbladder was diagnosed in four cases, but it was not associated in two of them. A wrong diagnosis of a perforating gastric ulcer was made once. No diagnosis was made in one case.

In the suppurative type of pancreatitis the diagnosis was made correctly twice. The diagnosis was partly correct in a case of associated perforating duodenal ulcer once and of a perforating gallbladder once. No diagnosis was made in four cases, and an incorrect diagnosis of an acute condition of the gallbladder was made in three cases.

In all cases of acute pancreatitis a correct diagnosis was made only eight times, or in 12 per cent. In eight other cases a correct diagnosis of an acute condition of the gallbladder or of a perforated viscus was made, but the pancreatitis was not suspected. The diagnosis was wrong in forty-eight cases, or 75 per cent. The most frequent mistaken diagnoses were: acutely inflamed gallbladder, perforating gastric or duodenal ulcer, acute appendicitis, carcinoma of the stomach or pancreas and acute peritonitis.

#### TREATMENT

In the sixty-four cases reviewed, no operation was performed on six patients, all of whom died. An exploration was done in seven cases, mostly type I pancreatitis, with an immediate closure without drainage; four of the patients died, or 57 per cent. Of the remaining fifty-one patients who were operated on, twenty-five, or 49 per cent, died.

Four chief procedures were followed at operation in the cases in which the wound was drained: (1) simple drainage of the peritoneal

cavity, chiefly in types I and II pancreatitis, with three recoveries and ten deaths, or a mortality of 77 per cent; (2) drainage of the pancreas or of an abscess within it in four cases in the suppurative type IV, with recovery in every case; (3) drainage of the gallbladder, which occasionally included the common duct, done in twenty-five cases, eleven patients recovering and fourteen dying, a mortality of 56 per cent, and (4) drainage of the gallbladder together with drainage of the pancreas or its capsule in nine cases, eight patients recovering, with a mortality of only 11 per cent.

This analysis would indicate that some drainage of the pancreas or its capsule should be introduced in all except perhaps the simple edematous type of acute pancreatitis. Drainage of the gallbladder alone does not always check a pancreatitis; therefore it is safer to institute prophylactic drainage of the pancreas in all cases, since it may prevent anaerobic infection or abscess formation. Biliary drainage is indicated in most cases with an associated jaundice and particularly with acute or chronic inflammation of the gallbladder or with gallstones.

If there is an abscess or infection in the pancreas, with an absence of obstruction or acute inflammation of the biliary tract, drainage of the pancreas alone should be sufficient. In the prophylaxis of acute pancreatitis one should remove all foci of infection, including the gallbladder in most instances of biliary tract disease, together with any gallstones (McWhorter<sup>103</sup>). Other important points are the avoidance of alcoholism and treatment for obesity.

Efforts have been made by Brocq to check the flow of pancreatic juice in acute pancreatitis by the use of atropine and also by neutralizing the acid chyme and thus to prevent the formation of secretin.

Immunization of animals has been attempted on the theory that death is due to a toxemia as a result of the action of trypsin. Ohno<sup>104</sup> has immunized animals by injecting activated trypsin into the peritoneal cavity and has obtained a highly immune serum, which has been used in four patients without ill effects. Schonbach<sup>105</sup> and Schonbauer have produced active immunization and immune serum experimentally.

While von Bergmann and Guleke<sup>106</sup> and Joseph and Pringsheim<sup>107</sup> were able actively to immunize against pancreatic necrosis

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103. McWhorter, G. L.: Preventive Surgery of the Pancreas and Bile Ducts, Illinois M. J. **47**:128 (Feb.) 1925.

104. Ohno, R.: Mitt. a. d. med. Fakult. d. k. Univ. Kynshu Univ. Fukusha (Japan) **7**:31, 1923; quoted by Brocq (footnote 3).

105. Schonbach, quoted by Brocq (footnote 3).

106. von Bergmann and Guleke: München. med. Wchnschr. **57**:1673, 1910.

107. Joseph and Pringsheim, quoted by Gross and Guleke (footnote 91, second reference).

through increased doses of trypsin and to lessen its intoxication, they were not able to obtain a serum from these animals for satisfactory passive immunity.

Spontaneous recovery may frequently occur in subacute pancreatitis (Moynihan and Mikkelson<sup>108</sup>). Resection of the necrotic portion of the pancreas has been done where the necrosis is limited to the distal portion (Hofmann<sup>109</sup> and Butler and Delprat<sup>110</sup>), but it is rarely indicated because of the difficulty in technic and the danger of hemorrhage and shock.

Körte reviewed 103 cases of acute pancreatitis, with a mortality of 60 per cent. He observed that more patients recovered who were operated on early in the first week, and he advised early operation.

Brocq reviewed 340 cases. Among 235 patients with acute hemorrhagic pancreatitis, 116 were operated on before 1910, with a mortality of 78 per cent, and 119 since 1910, with a mortality of 68 per cent. He believed that the mortality was lowered in many instances by supplementing drainage of the pancreas with drainage of the biliary tract.

In seventy cases of suppurative pancreatitis he noted a mortality of 51 per cent, and in thirty-five cases with subacute or edematous pancreatitis a mortality of 23 per cent. Drainage of the biliary tract in addition to drainage of the pancreas seemed to favor recovery, except in the suppurative form, in which drainage was associated with a higher mortality. There were seventy-seven patients with various types of pancreatitis on whom no operation was performed, and all died.

Early operative relief for biliary tension was emphasized by Archibald and Kaufman, who recommended biliary drainage even in subacute pancreatitis and in the absence of gallbladder inflammation. In addition, they advised drainage of the pancreas by a gauze drain, but warned against tearing the living tissue.

The performance of a cholecystectomy without biliary drainage is contraindicated because of the danger of subsequent increased biliary pressure and of prolonging the operation. In the mild cases, or exceptionally, cholecystectomy may be indicated. One is rarely justified in exploring for or attempting to remove a common duct stone, especially in the severe cases; one should merely institute biliary drainage. If exploration of the common duct is indicated, one should note whether the outlet is occluded or dilated. If the outlet is dilated, prolonged biliary drainage will not be indicated. In case of partial or total obstruction, due to congestion at the outlet, dilatation of the sphincter should

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108. Mikkelson, O.: *Hospitaltid.* **81**:132, 1925, quoted by Eliason and North: *Surg., Gynec. & Obst.* **51**:183 (Aug.) 1930.

109. Hofmann, A.: *Arch. f. klin. Chir.* **114**:1041, 1920.

110. Butler and Delprat: *Acute Hemorrhagic Pancreatitis*, *Surg., Gynec. & Obst.* **42**:379, 1926.

not be attempted, owing to the danger of increased swelling. If it is possible one may insert a small catheter through the common duct into the duodenum with a separate tube for the proximal drainage of bile. This will produce a further dilatation of the sphincter (McWhorter, 1921 and 1925) and will also permit the instillation of fluids into the duodenum (McArthur<sup>111</sup>). Under such conditions a further reflux of bile into the pancreatic duct is prevented and drainage of pancreatic secretion may occur around the tube into the duodenum.

Most surgeons strongly advocate early operation in all except the mild or the moribund cases of acute pancreatitis, although Mikkelsen defers operation until symptoms of diffuse peritonitis or abscess formation occur.

It is evident that the value of operative treatment depends on the type of pathologic condition present, but in most instances this can be determined only at operation. As a rule, the more severe the local and associated pathologic involvement, the more valuable will be properly executed operative intervention.

#### SUMMARY

The division of acute idiopathic pancreatitis into four pathologic types is of value in the study of this highly fatal condition. Obese patients and those with a history of persistent alcoholism have a greatly increased mortality.

Gross infection of the pancreas was found to be present more frequently in men. Some type of inflammation of the gallbladder or stones was present in 55 per cent of all cases, with little variation from the average mortality. Gallstones were present in fewer men than in women, although when present the mortality rate was identical. However, only 30 per cent of the men who died had gallstones, as compared to 53 per cent of the women. The higher mortality rate, 62 per cent, in men than in women, 47 per cent, indicates the presence of other factors than gallstones affecting the mortality. Acute inflammation of the gallbladder was present in only 22 per cent of all the cases. Evidences of obstruction of the common duct were found in a few cases. In two an impacted stone was found in the ampulla at necropsy.

There was little evidence of a regional or distant focus of infection existing before the onset of pancreatitis in any of the cases. In the majority of the cases of pancreatitis, pathologic changes were not found outside of the pancreas and the bile tracts. Gallstones, in addition to obstructing the ampulla, possibly may predispose to pancreatitis even when in the gallbladder, by disturbing the physiology of the biliary tract pressure and sphincter action. It is probable that regurgitation

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111. McArthur, L. L.: *Journal-Lancet* 36:723 (Dec. 15) 1916.



of bile into the pancreatic duct occurs rather frequently, and that there are contributing factors that modify the bile or otherwise contribute in producing acute pancreatitis.

Acute inflammation of the gallbladder may be a predisposing factor, but probably is more frequently a complication of pancreatitis. In many cases of acute pancreatitis pyogenic bacteria are found, but anaerobic bacteria are undoubtedly early invaders, especially when necrosis is present. There was a definitely lower mortality in the cases in which operation was performed immediately as compared to those in which operation was performed from the second to the fourth day after the onset of the disease. The mortality was also lower in a few cases in which it was performed at about the end of the second week.

When suppuration of the pancreas or inflammation of the gallbladder was present, the mortality was lower in cases in which early operation with appropriate drainage was performed. However, there remained an unusually high mortality in cases in which both an acute inflammation of the gallbladder and necrosis or suppuration of the pancreas were present.

Since all of the patients not operated on died, it is evident that early diagnosis is important, and should be followed by an emergency operation, unless the patients are moribund or definitely improving. Drainage of the pancreas should be established in all cases, except perhaps in the mild edematous type in which prophylaxis against infection may seem unnecessary.

Exploration of the biliary tract followed by drainage should be done in practically all cases, particularly in the presence of inflammation, gallstones or jaundice. In cases in which evident infection is localized in the pancreas, particularly after the first few days, drainage should usually be limited to the pancreas.

In a further effort to reduce the mortality, one must attempt to reduce the incidence of pancreatitis. This should include the prevention of and treatment for obesity, gallstones and foci of infection. Active or passive immunity may offer some hope for the future. Prophylaxis by the early removal of gallstones and well chosen operations on the gallbladder for acute and chronic cholecystitis may prevent hepatic, pancreatic and other serious complications.

## A REVIEW OF UROLOGIC SURGERY

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### KIDNEY

*Anomalies.*—Papin, Bernasconi and Bernard<sup>1</sup> reviewed the 27 cases of true supernumerary kidney reported in the literature. The relative frequency of the malformation could not be discovered, but it must be extremely rare. The supernumerary organ was on the right side in 12 cases, on the left in 14 cases and in the middle in 1 case. Nine occurred in females; 16 in males; in 2 cases the sex was not noted.

In some cases the kidney was only subjacent; in others, it was located at the iliac artery or the psoas muscle. The form was seldom indicated; in 1 case it was lobulated; in another, bean-shaped with convex anterior aspect. In the case of Bernasconi and Bernard the lower kidney was of normal shape, and the upper, supernumerary organ was concave on its lower surface, which fitted the rounded top of the lower kidney, the latter being lodged within it. The anomalous kidney was sound, and the normal kidney was diseased, having a stone in the ureter. The size of the kidney varied. In 2 cases the lower kidney was larger than the upper. In 10 cases there were only two ureteral orifices into the bladder, suggesting that the ureters were fused. In 2 cases the tract of the upper ureter was unusual; it dug a furrow in the supernumerary kidney before becoming fused with its ureter. In 1 instance the ureter of the supernumerary kidney turned upward and

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1. Papin, Bernasconi and Bernard: Contribution à l'étude du rein surnuméraire, Arch. d. mal. d. reins 6:1 (June) 1931.

entered the descending ureter of the upper kidney at the level of the superior pole of the lower kidney. In another case the two kidneys and their pelves had a single ureter, which passed from the upper to the lower and then to the bladder. In 11 cases there was complete duplication of the ureter. Two orifices opened into the bladder in 8 cases; the orifice was into the vagina in 2 cases and into the vulva in 1 case. In 1 case there were four ureteral openings into the bladder.

In 21 cases there were symptoms during life; in 6 cases the lesion was discovered at necropsy. There were three classifications of the cases: (1) a healthy supernumerary kidney, accompanied by pain or small concomitant malformations due to its abnormal position; (2) a diseased supernumerary anomaly, and (3) the association of some additional anomaly causing special symptoms. Certain cases were characterized by pain and an abdominal tumor. In 1 case the supernumerary organ was on the left side, but the pain was on the right. Usually calculi were present; these were sometimes in the normal kidney or its ureter.

Nephrectomy was performed in 16 of the cases. In 3 cases the transperitoneal route was used; in 8 the lumbar; in 3 cases two kidneys were removed by the lumbar route; in 1 case nephrostomy was done on one kidney, then two kidneys were removed by lumbar incision; in 2 cases nephrotomy was done for calculi.

The type of double kidney in which one kidney is invaginated into the other, designated by the authors as supernumerary kidney with impaction, is omitted from this consideration. The only cases included are those in which there are three separate parenchymatous masses of the kidney.

Jeck<sup>2</sup> stated that in 16,735 necropsies at Bellevue Hospital during the last twenty-six years, twenty-six horseshoe kidneys were found, one in every 643 cadavers. Necropsy statistics indicate that the life span of persons with horseshoe kidneys is relatively short.

The urographic characteristics on which a diagnosis of horseshoe kidney is based are mainly: renal pelves closer to the median line and lower than normally placed kidneys; shortening of one or both ureters; a tendency of the calices to point downward or toward the vertebrae, and calices of bizarre shapes, absence of calices or calices overlapping the pelvis.

Preoperative diagnosis of horseshoe kidney makes it possible to perform more easily and with greater facility whatever operation may be necessary than when the condition is encountered accidentally. Most surgeons with experience in operating on horseshoe kidneys prefer the extraperitoneal route to the transperitoneal. With an adequate incision and the extraperitoneal approach there is less likelihood of infecting the

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2. Jeck, H. S.: Horseshoe Kidney with Especial Reference to Surgical Technique; Report of Cases, *J. A. M. A.* 98:603 (Feb. 20) 1932.

peritoneum, especially when dealing with tuberculosis, pyonephrosis or infected hydronephrosis, and of reducing the probability of infecting the peritoneum in cases of pyelotomy or nephrotomy or in heminephrectomy, if the stump of the isthmus should subsequently secrete urine.

In considering heminephrectomy, the operation most frequently necessitated by the pathologic conditions found in horseshoe kidneys, the function and size of the other half of the kidney should be determined; also whether the other kidney has its own separate ureter, whether there are accessory arteries and veins, whether the kidney which is to remain has ample blood supply, and the size and composition of the isthmus. In ligating the renal pedicle, care should be taken not to tie the vessel or vessels which supply the only branch to the half of the kidney which is to remain. In 13 per cent of 60 cases studied at necropsy, Robinson found a single arterial trunk for the isthmus which divided, one branch supplying the right renal mass and the other the left.

Since 1918, in approximately 400 operations on the kidney in the Bellevue urologic service, there were 4 cases of horseshoe kidney. The condition was recognized preoperatively in 2 cases. In 3 of the cases, heminephrectomy was performed without any particular difficulty. The isthmus was small and chiefly fibrous; accessory blood vessels were also present, but were easily recognized. In the fourth case small bilateral calculi were removed from the right side by pyelotomy and nephrotomy; several days later secondary heminephrectomy became necessary because of hemorrhage.

Lazarus<sup>3</sup> stated that the anomaly of horseshoe kidney occurs in about 0.1 per cent of normal persons. There are no characteristic symptoms of horseshoe kidney; when they do occur they are caused by some associated pathologic lesion, to which they are more susceptible than normally formed kidneys. The diagnosis of this condition is usually made at operation or at necropsy. A flat renal roentgenogram will generally lead to the suspicion of this anomaly by showing the proximity of the kidney silhouette to the vertebral column, by the obliteration of the psoas margins in part or in their entirety and by the failure to visualize one or the other of the renal poles. The diagnosis may be corroborated by pyelography, showing the bizarre pelves and calices, usually pointing anteriorly and approximated to the median line, and shortening of the ureters.

Heminephrectomy is the preferred treatment for an extensive suppurative lesion, tumor or tuberculosis involving half of a horseshoe kidney. Other lesions are treated in the same manner as are similar diseases in normally formed kidneys.

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3. Lazarus, J. A.: Horseshoe Kidney: A Report of Five Cases, *J. Urol.* **27**: 471 (April) 1932.

[COMPILERS' NOTE.—The frequency of horseshoe kidney, as well as that of the associated lesions, has given rise to a definite clinical syndrome, recently described by Gutierrez. In a recent series of cases he has shown that the clinical diagnosis of horseshoe kidney can usually be obtained before operation by means of present-day proficiency in urography. The diagnosis was conclusively made in 19 of 25 cases studied by Gutierrez<sup>4</sup> in which a urologic examination was made. Jeck has correctly emphasized the fact that the extraperitoneal route of surgical approach is the safer, and that the transperitoneal method of exploration employed in the days before urography must not be used on account of the possibility of peritoneal infection.]

In some cases there is a definite indication for symphysiotomy, or the division of the isthmus of the horseshoe mass, followed by nephropexy. This insures better drainage of the kidney and helps to eliminate the symptoms associated with fusion, which are usually due to the median line situation of the organ, even though a lesion is not present.]

*Tumors.*—Hager<sup>5</sup> stated that the syndrome of tumor, pain and hematuria occurs late in the course of renal tumors. He pointed out that the early symptoms are vague, and urged repeated examination in such cases. Repetition of all the tests of renal function with retrograde and intravenous pyelography should yield a diagnosis in early suspicious cases. The significance of renal displacements and irregularities in contour in the roentgenogram is emphasized. If all signs fail and a tumor is still suspected, an exploratory operation should be done. Seventeen cases of renal tumor are reported, 2 of which occurred in children. Pyrexia was a prominent symptom in 4 of the 15 adults and in both children. Three of the adults had metastasis. The diagnosis was confirmed in every case by operation.

[COMPILERS' NOTE.—The incidence of pyrexia in these cases is rather unusual. As the author pointed out, an occasional high temperature is at times striking and a significant symptom. It occurs in approximately 10 per cent of reported cases. In some cases the fever is suggestive of metastasis and may be associated with severe, widespread bodily pains. In a case reported in which marked pyrexia was present before removal of the kidney, the reappearance of a high temperature was the first symptom indicating recurrence and metastasis.]

Darmady<sup>6</sup> stated that squamous cell carcinoma is the rarest type of malignant growth of the renal pelvis. Up to 1924 only 60 cases of

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4. Gutierrez, Robert: The Clinical Management of Horseshoe Kidney, *Am. J. Surg.* **14**:657 (Dec.) 1931; **15**:132 (Jan.); **15**:345 (Feb.) 1932.

5. Hager, Ilse: Beitrag zur Diagnostik der Nierentumoren, *Berl. Klinik* **38**: 1, 1931; abstr., *Am. J. Cancer* **15**:3023 (Oct.) 1931.

6. Darmady, E. M.: Squamous-Cell Carcinoma of the Renal Pelvis, *St. Barth. Hosp. J.* **38**:118 (March) 1931.

this lesion were reported in the literature; 6 cases have been reported since then, making a total of 66. Numerous cases have been ascribed to renal calculi of long standing, but Miller and Herbst have shown that of 54 cases in which an examination was made, only 10 can be attributed to renal stone. Cumming stated that the normal transitional epithelium can become replaced by a many-layered coating of stratified squamous epithelium with superficial keratinization. This condition of leukoplakia is associated with infection, stone and hydronephrosis.

Darmady reported a case of squamous cell carcinoma of the renal pelvis in which an operation was performed in 1930. Hydronephrosis had been present twenty-eight years before. The size, weight and striking lamination of a calculus removed at operation indicated that the latter had also been present for a number of years.

Stux<sup>7</sup> reported a case of teratoma of the right kidney of an infant aged 9 months. The growth had been noticed in the right side of the abdomen one month previously and had increased rapidly in size until it reached from the ribs to the iliac crest and mesially to the median line. It was smooth, oval, not tender and fluctuant. Repeated urinalysis showed traces of albumin and the constant presence of a few erythrocytes. At operation the mass was found to be cystic, and could be removed only after several of the cysts had been punctured. The child died two days later of pneumonia. At necropsy, the left kidney did not contain a tumor.

Pathologic examination revealed that the tumor arose from the upper and inner portion of the right kidney. In a collapsed state it measured 11 by 8 by 7 cm. and weighed 368 Gm. The entire mass was well encapsulated; its surface was slightly lobulated. On section numerous cysts of various sizes were found, separated by a small amount of compact cellular tissue. Microscopically the cysts were lined with high cylindric or cuboidal epithelium. The supporting connective tissue was infiltrated with small round cells which showed numerous phases of mitosis. The diagnosis of an embryonal mixed tumor of the kidney was made.

[COMPILERS' NOTE.—Most tumors of the kidneys of children occur during the first two years of life. The pelvis of the kidney is generally not involved; consequently urinary symptoms and pain are rare. These neoplasms grow rapidly; the increase in size is generally due to intrarenal hemorrhage. The average length of life after the onset of symptoms is about eight months; following nephrectomy it is from sixteen to twenty months. Death is almost certain if operative procedures are

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7. Stux, Herbert: Zur Frage über die malignen Nierentumoren im frühen Kindesalter, *Arch. f. Kinderh.* 92:128 (Dec. 19) 1931; abstr., *Am. J. Cancer* 15:3025 (Oct.) 1931.

not carried out. Nephrectomy often prolongs life and offers the only chance for improvement. Earlier writers all agree on the unusually high mortality rate.

Stux designated his case as that of teratoma of the kidney. These growths usually have the same characteristic histologic structure. The predominating structures are groups of incompletely formed glands surrounded by masses of irregularly disposed cells. They may contain striated muscle, squamous cell nests and, more rarely, areas of bone and cartilage.]

*Stone.*—Schultheis<sup>8</sup> stated that the origin of urinary calculi, especially that of renal stones, is still unknown. The following theories have been assumed: (1) disposition of the particular organism to formation of stone, either a uric acid or phosphate diathesis, or other factors such as geographic, alimentary or exogenous influences, and (2) a changed excretory threshold, such as disturbance of the intermediary cell product exchange of the kidney which causes a change in the colloidal equilibrium of the urine and results in a precipitation of crystalloid elements.

The pathologic histology does not show any primary changes in either the renal parenchyma or the lower part of the urinary tract by which the formation of stone can be explained. The histologic changes in kidneys containing stones are secondary to the calculi.

Schultheis is of the opinion that calculi originate in the pelvis and when found in the calices, have emigrated there. A kidney with a stone has a lowered resistance and may be infected by either the lymphogenous, hematogenous or urogenous route. A movable stone may lead to pressure changes between Bowman's capsule and the glomerulus. When a stone migrates to the pelvis, there may be obstruction leading to intermittent hydronephrosis or pyonephrosis. Clinically, stones are either aseptic or infected. In the former case the condition is usually acute, with stasis and pressure changes, whereas in the latter there is destruction of the organ, depending on the virulence of the organism.

Gottstein classified the pathologic anatomy of kidneys containing stone as follows: (1) the normal appearing kidney, (2) the atrophic kidney, (3) the so-called perirenal fat kidney (replacement lipomatosis) and (4) the calculous hydronephrotic and pyonephrotic kidney.

From a study of 26 cases of renal stone the following conclusions were drawn: There is usually pyelitis of varying degrees, depending on the size of the stone, and limited renal function and associated infection. In the aseptic cases there may be glomerulotubular nephritis with more atrophic tendencies, whereas in infected cases there is more or less

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8. Schultheis, Theodor: Histologische Untersuchungen an Steinnieren, *Ztschr. f. urol. Chir.* **31**:193 (March) 1931.

inflammation present, the interstitial tissue being partly atrophic, edematous and hypertrophic. Occasionally there are individual cases with notable changes in vessels, such as sclerosis of the arteries. There is the small inflammatory group characterized by an increase in the fibrous and fatty capsules.

[COMPILERS' NOTE.—In spite of an enormous volume of literature and an extensive amount of laboratory investigation with the experimental production of calculi in animals, we have as yet a very incomplete understanding of the pathologic changes incident to the formation of stone. As brought out by Schultheis, altered anatomic changes in the kidneys are not consistent or of especial significance in clarifying the problem. Inflammatory reactions, atrophy and the features associated with stasis comprise the details of the picture. Certainly the presence of stone lowers renal resistance and renders the affected kidney liable to the pathologic changes associated with chronic and acute infection, sclerotic processes and, at times, neoplasia.]

Braasch<sup>9</sup> stated that repeated recurrence of renal stone is not common, and if it does occur, etiologic factors are present other than those causing the usual single or occasional calculi. In a review of the postoperative results in more than 1,000 cases of nephrolithiasis at the Mayo Clinic, he found that stone recurred in approximately 10 per cent of the cases. There was recurrence subsequent to a second operation in only a few cases, approximately 2 per cent.

The exact factors involved in the etiology of lithiasis are still unknown. Opinions are divided as to whether the condition is caused by abnormal metabolism or infection, while there is reason to believe that both factors may be involved. It is generally accepted that abnormal metabolism is the usual cause of recurrent stones composed of uric acid, cystine and xanthine, as shown by the fact that uric acid stones cease to form when the patient is placed on a purine-free diet. The repeated formation of stone may also be due to infection, such as occurs with urea-splitting bacteria. Bacteriologic studies at the Mayo clinic by Hager and Magath have shown that infection with *Proteus ammoniae* is often the direct etiologic factor in the formation of phosphatic stones. That some anatomic factor causing retention in a calix, the renal pelvis or the ureter may be a primary factor permitting such infection is also possible. Most recurring stones of this type are composed largely of calcium phosphate. Renal stones composed of fibrin are exceedingly rare, particularly in cases in which stones form repeatedly.

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9. Braasch, W. F.: Recurring Renal Lithiasis, Proc. Staff Meet., Mayo Clin. 7:169 (March 23) 1932.



nephrectomy resulted in cure in only 47 per cent. Nine per cent of patients with coexisting pulmonary tuberculosis died following operation, and only 29 per cent recovered completely. Lesions of bone have the least effect on the ultimate results: In 62 per cent of 18 cases complicated by lesions of bone, complete recovery occurred. In 59 per cent of 12 cases of genital lesions, recovery took place. Persson<sup>12</sup> reported 295 cases from the Seraphimer Hospital, Stockholm. Symptoms of other tuberculous lesions occurred in about half the cases as follows: pulmonary tuberculosis, 66 cases (22.4 per cent); tuberculosis of genitalia (male), 46 cases (15.6 per cent); tuberculosis of bones and joints, 21 cases (7.1 per cent); pleuritis, 7 cases, and lymphadenitis, 10 cases. There were 84 cases in Persson's series in which operation was not done. Death occurred in 71 cases (84.5 per cent). In Wildbolz'<sup>13</sup> large series of cases, more than half of the patients who had been traced from ten to twenty years following nephrectomy died of tuberculosis of the remaining kidney or of pulmonary tuberculosis. Rovsing and Frode<sup>14</sup> reported 632 cases of renal tuberculosis; 62 per cent of the patients were well following nephrectomy. Death usually occurred within the first year after nephrectomy and, as in Wildbolz' cases, was generally due to tuberculosis of the remaining kidney or other organs.]

Papin and Bordas<sup>15</sup> reviewed 400 cases of hematuria which followed nephrectomy for tuberculosis of the kidney. The hematuria was classified according to the time of appearance: immediately following operation, during the course of the postoperative period and weeks, months or even years afterward. The hemorrhage may come from the ureteral stump, from the opposite kidney or from the bladder. It is generally slight and attracts little attention. In the early days following operation it is reasonable to believe that it was the remaining kidney that was bleeding. This cannot be demonstrated positively, as cystoscopy at this time should not be done unless it is absolutely necessary. The third type of hemorrhage occurs most frequently and is invariably from the bladder. In many cases the lesions have become worse after nephrectomy, sometimes becoming so serious that it has been necessary to exclude the bladder by an iliac ureterostomy. Occasionally hemorrhage from the bladder appears after conditions have quieted and the symptoms have disappeared or improved. This does not usually indicate that the second

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12. Persson, Mauritz: Renal Tuberculosis: A Clinical Survey of 295 Cases, 90 of Which Were Not Operated On, *Ann. Surg.* **82**:526 (Oct.) 1925.

13. Wildbolz, Hans: Renal Tuberculosis, *J. Urol.* **21**:145, 1929.

14. Rovsing, Thorkild, and Frode, Rydgaard: Klinische Untersuchungen über die Tuberkulose der Harnwege, *Bibliot. f. læger* **117**:225, 1925; abstr., *Ztschr. f. urol. Chir.* **19**:415, 1926.

15. Papin, Edmond, and Bordas, Paul: Des hématuries chez les sujets néphrectomisés pour tuberculose rénale, *Arch. d. mal. d. reins* **6**:413, 1932.

kidney has become affected; iliac ureterostomy in grave cases has generally demonstrated the integrity of the remaining kidney.

Pascual<sup>16</sup> reported a case of tuberculous kidney in a man aged 37 years. There were no clinical symptoms, but roentgenograms revealed a complete shadow of the caseous and calcified organ as well as of the entire ureter from the kidney to the bladder. On cystoscopic examination the mouth of the left ureteral orifice was obliterated; the right side was normal. The bladder had normal capacity, and there was no ulceration or other signs of tuberculosis present. The kidney and ureter were removed, and a good result was obtained. The specimen proved to be a caseous tuberculous kidney with complete distortion and calcification of the organ and its thick blind ureter. The impression of petrified deposits occupying and obliterating both the kidney and the entire lumen of the pelvic ureter was obtained from the roentgenogram.

Pascual stated that this case indicates the need for complete urologic examination when dealing with a suppurating kidney, even though the premonitory symptoms have subsided and the silent kidney has undergone almost complete obliteration.

[COMPILERS' NOTE.—Renal occlusion occurs in about 10 per cent of the cases of chronic renal tuberculosis. Braasch stated that it can be recognized in about 90 per cent of cases. Symptoms such as pain, frequency and abdominal tumor may extend over a period of many years. The occluded kidney may be a focus of infection, especially if of recent occurrence. In several cases in which symptoms had been present for many years and the kidney occluded for from five to ten years, the bacillus of tuberculosis was found in the renal mass. If symptoms are present, nephrectomy is indicated; usually there is little risk in operating and good results are obtained, as satisfactory resistance to the infection has developed.]

Dossot<sup>17</sup> stated that tuberculosis of the kidney and of the renal excretory ducts may be easily confused. The latter is seldom present without participation of the renal parenchyma, but since the initial localization of the Koch bacilli is usually the point where the calices are inserted around the papillae, the lesions generally extend into the renal pelvis, ureter and bladder at the same time. Primary tuberculosis of the pyelo-ureteral tract is rare; approximately 12 cases only have been reported in the literature. In pyelo-ureteral tuberculosis the only constant lesion is ulceration of the lateral part of one or more papillae. The earliest lesions are in the noncaseous tuberculous follicles

16. Pascual, Salvador: Caseous Kidney, *An. Hosp. de San José y Santa Adela (Cruz Roja) Madrid* 2:135, 1930-1931.

17. Dossot, R.: Tuberculose pyélo-urétérale, *Arch. urol. de clin. de Necker* 7:135 (Dec.) 1931.

under the epithelium in the lateral portion of the papilla. As these lesions progress, they rapidly produce changes in the contractility of the pelvis and ureter, followed by modifications in the ability to evacuate the contents of the pelvis. After removal of a tuberculous kidney, tuberculosis of the ureter tends to regress and disappear, with the ureter contracting into a fibrous cord. There are cases in which the ureteral stump may give rise to further disturbances, such as persistence of cystitis and pyuria, purulent lumbar fistulas, urinary fistulas and formation of ureteral abscesses. To avoid these complications, two methods have been used: extirpation of the ureter at the time of nephrectomy; and simple nephrectomy followed by suitable treatment of the ureteral stump. Nephro-ureterectomy entails so much risk in cases in which the ureters are bound by inflammatory adhesions that it is not desirable; even when the patient recovers, postoperative fistulas are common. Systematic ureterectomy has been generally abandoned in favor of such measures as fixation of the stump to the abdominal wall, suture of the upper orifice of the ureter, or ligation and cauterization of the stump. All of these procedures are of doubtful value. Dossot prefers the technic of Leguen: section by thermocautery, between two clamps, of the ureter in the lower part of the lumbar wound; ligation of the ureter with catgut, and drainage if the perinephritis is intense, if pus has contaminated the region or if the surface of the kidney presents granulations. In the absence of such conditions, the wound is closed completely after the cavity has been filled with isotonic dextrose solution.

[COMPILERS' NOTE.—It is true that primary ureteral tuberculosis is seldom seen, because the original lesion is established in the kidney and the ureter becomes infected by the excretory bacilluria. The tuberculous ureter is the result of tuberculosis elsewhere in the upper part of the urinary tract, and when severe infection of the pelvis and ureter has been found, in a certain number of cases the conservative and safe procedure is to perform ureteronephrectomy in order to obviate lumbar fistula, pyuria, tuberculous cystitis and other common sequelae. Kelly, Beer, Gutierrez, Papin, Judd and others heartily recommend this technic and have reported good clinical results without complications or fatalities. The technic of the operation of ureteronephrectomy in two stages is simple and may be carried out without difficulty; the results achieved justify its recommendation. Gutierrez<sup>18</sup> has recently described this operation.]

Katz<sup>19</sup> stated that tuberculosis is widespread not only among domestic fowls but among other birds, in various percentages. It usually

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18. Gutierrez, Robert: *Indications and Technic of Combined Ureteronephrectomy*, *Ann. Surg.* **93**:511 (Feb.) 1931.

19. Katz, Traian: *Tuberculose urogénitale chez l'homme produite par le bacille de la tuberculose aviaire*, *J. d'urol.* **31**:18 (Jan.) 1931.

affects the spleen, liver and intestinal tract. The kidneys are frequently involved, and in such cases localized or disseminated nodules are present. The bacillus differs from the human bacillus bacteriologically, morphologically, culturally and biologically. It grows more rapidly (in from ten to fourteen days) and at temperatures between 26 and 46 C.; the cultures are small, moist, abundant, mucofatty and slightly detachable, with a vitality far greater than that of the analog from human beings. The first case in man was published by Lipschutz in 1914, and 5 others have been reported since then. Katz has observed 2 cases, and concluded that the bacillus produces in man a septicopyemic disease known as morbus Löwenstein. It begins with fever (from 38 to 39 C. [100.4 to 102.2 F.]) which is not influenced by antipyretics. The general condition is not especially affected by this fever. Night sweats suggesting pulmonary tuberculosis and enlargement of the spleen are observed. After this phase, which may last months or years, localization is reached, with the site of predilection in the kidneys, bone marrow and the skin. Small yellow nodules from 1 mm. to 1.5 cm. in size are found in the kidneys; in rare cases there is cavity formation with caseation. Diffuse cystitis is characteristic but without specific lesions. The presence of large numbers of acid-fast bacilli with the polymorphonuclear leukocytes is always suggestive of tuberculosis of avian origin. Their portal of entry is probably through the mouth, with the ingestion of food, particularly eggs containing the bacilli. Löwenstein infected hens' eggs with avian bacilli, boiled the eggs and later recovered living bacilli from the hard-boiled eggs. Histologically, the affected tissues do not exhibit tuberculosis but abscesses and disseminated necrobioses. If treated early, these patients are readily cured by injections of avian tuberculin. Spontaneous cure occurred in 1 case on record.

*Cysts.*—Covisa<sup>20</sup> emphasized the rarity with which hydatid cysts are localized in the genito-urinary organs. The highest estimate places them at 7.97 per cent of all such cysts. In 14,000 cases of genito-urinary disorders at the Provincial Hospital and in Covisa's private practice, there were only 9 cases of hydatid cyst, 4 of which were in the kidney and 5 retrovesicoprostatic. These four were open cysts in the renal pelvis, and were easily diagnosed. The symptoms were intermittent and sudden intense abdominal pains, followed by expulsion of foreign bodies resembling the seeds and skins of grapes. Eosinophilia was 5, 7 and 8 per cent in cases in which it was investigated.

Hydatid cysts may be opened or closed. The latter are difficult to diagnose, as they give few symptoms to distinguish them from other abdominal tumors. If small they are not noticed for some time and do

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20. Covisa, I. S.: Hidatidosis genitourinaria, *Rev. españ. de cir. y urol.* **12**:552 (Dec.) 1930.

not cause symptoms; even when they are large the characteristic hydatid tremor cannot always be recognized. The diagnosis is based on investigation of eosinophilia and fixation of complement, which is frequently positive. The closed cysts may become infected through the circulation of the blood and suppurate, complicating the symptoms by deep infection with intermittent fever and sudden profuse sweating, suggestive of closed pyonephrosis. When the cyst ruptures into the renal pelvis, the daughter cysts present the clinical picture of nephritic colic and are expelled in the urine. The tumor becomes reduced in size, but the cysts generally fall a prey to infection, and pyonephrosis develops, which ends by destroying the entire renal parenchyma. The formation of firm perinephritic adhesions then renders operative procedure difficult.

Treatment is necessarily surgical. The methods used have ranged from simple puncture to marsupialization of the cystic pouch, after sterilization of its contents, the evacuation and capitonnage of the cyst and its extirpation with or without simultaneous nephrectomy. The procedure chosen must depend on the intrinsic conditions of the cyst, such as its size, adhesions and relations to the kidney and its pelvis. A cyst can rarely be removed in one piece because of adhesions. Small cysts may sometimes be removed by partial nephrectomy. Large cysts usually require marsupialization, but the tendency of purulent or urinary fistulas to form must be borne in mind. Recurrence is common. Nephrectomy should be done by the lumbar route in order to avoid infection. It is the method of choice when partial nephrectomy is impossible and marsupialization is not necessary, for it has the advantage of prompt and radical cure without recurrence, provided the contents have not ruptured into the perirenal tissues.

According to the literature, retrovesical hydatid cysts are more rare than renal cysts. They may cause grave urinary disturbances, and are generally recognizable by the fact that the hypogastric tumefaction persists after catheterization of the bladder. If there is suppuration, diagnosis is more difficult, small cysts being easily confounded with abscesses of the prostate gland and seminal vesicles. These cysts may be due to a generalized peritoneal hydatidosis, or they may be the sole peritoneal localization. The prognosis is more favorable in the latter instance. The treatment of choice is marsupialization, preferably hypogastric. The retroperitoneal evolution of the cyst may make the perineal route more convenient in some cases. Its complete extirpation in a mass is generally not feasible because of adhesions. Eight clinical cases are reported.

Munger<sup>21</sup> stated that the hemorrhagic type of cysts of the kidney are caused by hemorrhage into a cyst of varied origin, and that such

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21. Munger, A. D.: Acute Hemorrhagic Cyst of Kidney, *J. Urol.* **27**:73 (Jan.) 1932.

lesions should be grouped according to the histogenesis. A case of a cyst of lymphogenic origin, with hemorrhage, is reported by Munger. These cysts are relatively rare and do not present a characteristic syndrome. Treatment is surgical; nephrectomy is preferred when resection is not possible.

*Carbuncle.*—Brady<sup>22</sup> stated that carbuncle of the kidney is caused by metastatic staphylococcal infection, which frequently is limited to the cortex; the pelvis of the kidney is not involved. The infection is usually secondary to furuncle, abscess or carbuncle of the skin or subcutaneous tissue. The typical carbuncle is composed of many small suppurating areas, and the whole lesion is separated from the remainder of the kidney by a definite ring of inflammatory tissue. Perinephritic abscess often develops from the carbuncle. It is the belief of some surgeons that all perinephritic abscesses arise in this manner, although the cortical lesions are not always detected. Microscopic examination of a carbuncle of the kidney shows lymphocytes, plasma cells and polymorphonuclear leukocytes. Staphylococci are usually scattered through the tissues.

A study of the literature revealed 88 reported cases of carbuncles of the kidney. The lesion occurred most frequently between the ages of 20 and 40 years. Fifty-four carbuncles occurred in men and 21 in women. In 13 cases the sex was not recorded. In 73 cases there was a definite history of a primary focus from which organisms could be carried to the kidney, and in 3 others there was a history of trauma to the side on which the carbuncle developed. The usual time between the onset of the primary focus and the carbuncle of the kidney was one month, although there were a few cases in which seven months elapsed between the onset of the primary focus and the development of the carbuncle of the kidney.

The onset of symptoms of this disease is usually acute; occasionally they appear gradually. Sometimes the temperature is elevated for a month before any renal lesion is indicated. On palpation there is localized tenderness over the involved kidney, and later a mass can often be felt. Cystoscopy in 23 cases did not disclose any abnormality in the appearance of the bladder and ureteral orifices. In almost every instance in which a differential phenolsulphonphthalein test was done there was delay in the appearance of the dye from the affected side, and diminution of the phenolsulphonphthalein excreted from the kidney containing the carbuncle as compared to the other kidney. In 43 cases it was noted that a perinephritic abscess was present. Positive cultures were obtained at operation directly from the carbuncle in 65 cases. The records do not

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22. Brady, Leo: Carbuncle of Kidney (Metastatic Staphylococcus Abscess of Kidney Cortex), J. Urol. 27:295 (March) 1932.

indicate whether cultures were taken in the remaining cases, but there is no mention on this subject of a negative culture being obtained from a renal carbuncle. In 45 cases *Staphylococcus aureus* was present; in 3 cases, *Staphylococcus albus*; in 14 cases the type of staphylococcus was not reported.

In 39 cases nephrectomy was performed at the first operation. There were 3 deaths (7.7 per cent). In the 45 cases in which different conservative procedures were carried out, there were 5 deaths (11 per cent). Four of the 5 patients who died were treated by incision and drainage of the carbuncle, and the fifth was treated by enucleation of the carbuncle and later by nephrectomy. Two of the 5 patients on whom nephrectomy was performed after a primary conservative operation died. Five patients treated by excision of the carbuncle and 2 whose kidney was incised and soaked in a flavine dye recovered. In Brady's personal case the renal capsule was divided through its entire length and drained down to the carbuncle; the result was satisfactory.

Brady's conclusion, after reviewing these 88 cases of renal carbuncle, is that no definite rules can be drawn for the precise operation indicated. He favors some type of conservative procedure; in a large number of cases the kidney can be saved by incision and drainage of the infected area.

MacMyn<sup>23</sup> described carbuncle of the kidney as staphylococcal suppurative nephritis, the result of hematogenous metastatic infection of the parenchyma of the kidney following a suppurative lesion of the skin such as a boil, whitlow or carbuncle. It produces a localized necrotic zone in the renal substance with multiple suppurative foci, and later circumscribed abscesses form with enlargement of that part of the kidney involved in the infectious process.

The onset of the symptoms is gradual; headache, fever and malaise appear several weeks after the primary infection. Lumbar pain in the side involved, with tenderness and rigidity, appear later. Usually there are no urinary symptoms, and because the lesion does not communicate with the renal pelvis or calices the urine may be normal. Pyelograms may be negative, although if the condition is advanced there will be a compression defect or distortion of the calices. The significant diagnostic facts are the history of infection of the skin, the gradual onset of malaise, fever, pain and tenderness in the lumbar region and comparatively normal urine.

Nephrectomy is usually indicated. More conservative measures, such as drainage, enucleation or heminephrectomy, are not sufficient, and subsequent nephrectomy is almost always necessary. More careful explora-

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23. MacMyn, D. J.: Carbuncle of the Kidney, *Brit. J. Urol.* 4:11 (March) 1932.

tion during operations for perinephritic abscess will show a higher percentage of carbuncles of the kidney than have been previously reported.

*Rupture.*—Pedroso<sup>24</sup> reported on closed traumatism of the kidney, that is, injury in which there is no external wound of the integuments of the organ. The injury may be caused by direct or indirect contusions, the form depending on the force of the blow, the resistance offered and the point of support. In 1 of 2 cases, a boy, aged 10 years, apparently received abdominal injuries by a fall. Laparotomy done twice did not disclose trauma of any abdominal organ, but the second operation established the presence of a huge retroperitoneal tumefaction occupying the renal fossa on the left side, which had not been present at the time of the first operation. Three weeks after the injury, nephrectomy was performed and an infected hydronephrotic sac was found. The unusual feature of this case was the apparent rapidity with which traumatic hydronephrosis developed, and also the fact that the kidney was in a state of advanced atrophy only three weeks after the lesion had occurred.

As a rule, authors deny the possibility of primary traumatic hydronephrosis. Proof of the existence of the condition in this case is demonstrated by the fact that prior to the accident there were no symptoms; that at the first laparotomy there was no tumor; that the tumor doubled in size during the four days preceding nephrectomy, showing the rapidity of its growth, and that at nephrectomy, three weeks after the injury, the tumor contained the multiple cavities with condensation of parenchyma characteristic of hydronephrosis. Pedroso is of the belief that the mechanism of this hydronephrosis lay in the obstruction of the ureteral orifice by blood clots. Expectant treatment is justified only in benign cases. In every case of renal tumefaction, internal hemorrhage of forty-eight hours' duration or persisting slight hematuria, surgical intervention should be carried out.

Lazarus<sup>25</sup> stated that hydronephrotic kidneys are more prone to spontaneous and traumatic rupture than normal kidneys. Henline found only 24 cases of spontaneously ruptured kidneys reported in the literature; 19 of these patients were operated on, and 7 died. The 5 patients not operated on died. Spontaneous rupture of kidneys may be due to mild forms of trauma, which may be easily overlooked by patients. The rupture occurs rarely, as indicated by the few cases reported in the literature. Kidneys of children which rupture as a result of mild trauma are usually hydronephrotic.

24. Pedroso, Gonzalo: Closed Traumatisms of the Kidney, *An. d. cir.* 3:112 (March) 1931.

25. Lazarus, J. A.: Traumatic Rupture of Congenital Hydronephrotic Kidney, *Ann. Surg.* 95:117 (Jan.) 1932.



Exploratory laparotomy is indicated in cases in which there is doubt regarding the presence of an intra-abdominal lesion associated with the renal injury. The kidneys should be exposed and explored through a second incision in the loin. Conservative surgical measures cannot be used in cases of rupture of congenitally hydronephrotic kidneys; nephrectomy is the procedure of choice.

*Nephritis.*—Simons<sup>26</sup> stated that surgical intervention is indicated in selected cases of acute and chronic nephritis in which one or more of the following symptoms are present: severe renal pain, massive renal hemorrhage, the oliguria-anuria-uremia complex and the preceding symptom associated with anasarca.

Complete urologic examination should be made in order to eliminate conditions such as hemorrhage with tuberculous kidney, calculous anuria, neoplasm of the kidney or its pelvis and other conditions which are not true manifestations of nephritis.

Most of the cases which are considered as surgical are classified in the groups as acute diffuse glomerulonephritis, chronic diffuse glomerulonephritis, the kidney of pregnancy and eclampsia, necrotic nephroses, lipoid nephroses, embolic purulent nephritis and focal and unilateral nephritis. Renal decapsulation, nephropexy, nephrotomy and nephrectomy are indicated in selected cases. Simons emphasized the point that the various forms of chronic nephritis without anuria are not suitable for decapsulation. In the early history of renal surgery Edebohls, Guiteras and others advocated this procedure in these cases and to a certain extent brought the operation of decapsulation into disrepute.

Randall, in considering nephritis, cited the recent work of Richards in regard to nephritis which accompanies poisoning with corrosive mercuric chloride. In Richards' experimental work it is pointed out that the primary effect is destruction of tubular epithelium. Tubules are filled with their own detritus, a process which continues for about ten days, during which time there are symptoms of anuria and increasing changes in the chemical composition of the blood. Usually with the administration of increased fluids these tubules gradually empty themselves, and the anuric state is terminated. It was observed that, although clinically the anuria was ended and urination was apparently normal, the chemical changes in the blood increased and reached a maximum only in about three or four days after the anuria had been broken. Richards' explanation of this is that when the tubules have been washed free of cellular detritus they are almost denuded of epithelium. Glomerular fluid coming down and passing through the tubules is separated from the vascular bed of the kidney by a thin membrane, and

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26. Simons, Irving: The Surgical Treatment of Nephritis, *J. Urol.* **27**:399 (April) 1932.

a vicious cycle is created whereby the tubular fluid is immediately reabsorbed. In spite of the elimination of urine, there is no excretion of metabolic products, so for several days after the end of the anuria the chemical constituents of the blood may be expected to increase.

[COMPILERS' NOTE.—Renal decapsulation, nephrotomy and renal denervation are major procedures which have been tried with variable success for a number of years in treating nephritis. The operations have never become popular. Simons' extensive review of the subject is timely and in general agreement with the study by Rovsing published a few years ago. Undoubtedly the good results cited in selected cases of acute and chronic glomerulonephritis, in cases of pregnancy and eclamptic nephritides, in cases of massive hemorrhage and in general when the oliguria-anuria-uremia syndrome is present, with or without anasarca, will stimulate interest in chemical changes.

Randall's<sup>27</sup> presentation of Richardson's excellent hypothesis as to the cause of increasing retention of metabolite in the blood during the early phase of diuresis following poisoning by mercury offers a satisfactory explanation of this curious clinical paradox.]

*Regurgitation.*—Lewis<sup>28</sup> stated that urinary regurgitation has scarcely been mentioned among writers as a cause of sudden and severe renal colic without the source of it being discovered. Kelly and Burnham found records of more than 100 operations being performed, nephrectomy among them, for relief of this type of pain without discovering the etiology and without disappearance of the symptoms in many cases.

The pain is sudden and severe, at times requiring an opiate for relief; the attacks may recur at varying intervals. Examination by roentgen rays or ureteral catheterization fails to reveal any ureteral calculi.

Lewis has identified the etiologic factor in the majority of these cases as definite obstruction at the neck of the bladder. Removal of this obstruction has invariably given relief of the condition. The connection between obstruction at the vesical neck and renal colic was at first ascribed to reflex nervous influence. Since then it has been demonstrated that even a moderate amount of intravesical pressure is capable of overcoming the resistance of the ureteral valvular orifices and permitting the regurgitation of urine or fluid up into the ureters and renal pelves. The belief that this regurgitation causes the pain or colic has been confirmed by clinical results.

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The diagnosis of this type of renal colic depends on conditions favoring back pressure and regurgitation through the ureteral orifices plus the inability to demonstrate the presence of stone in the ureter. If severe straining at urination with an over-filled bladder, accompanied by pain in either flank, indicates the presence of residual urine and there is no evidence of stone, a complete urologic examination should be made.

The prognosis of regurgitation colic depends on the removal and control of the obstructing factor.

[COMPILERS' NOTE.—Lewis deserves great credit for calling the attention of urologists to such an important and quite universally overlooked condition. In direct line with his consideration of this problem is the fact that renal colic from regurgitation in cases in which the ureteral meatus has been divided in the procedure of ureteral meatotomy causes distressing pain; on this account the operation is now avoided whenever possible. Doubtless back pressure from obstruction of the vesical neck has been overlooked as a cause of ureteral and renal pain, the basis being the mechanism which Lewis described.]

*(To be Continued)*

## THE BREAKING STRENGTH OF HEALING FRACTURED FIBULAE OF RATS

### V. OBSERVATIONS ON A LOW CALCIUM DIET

R. M. McKEOWN, M.D.

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NEW HAVEN, CONN.

The mobility of the calcium and phosphorus of bone has been demonstrated in recent years to be much greater than we formerly thought,<sup>1</sup> and it has come to be recognized that it probably is this increasing and decreasing salt content of bone that is responsible for the fluctuations that we have observed in its breaking strength.<sup>2</sup> The pliable bone of youth and the brittle chalky bone of the aged have for a long time been considered as differing in their respective strengths because of variations in their mineral content, but it has been only lately that we have been able to show that years are not necessary for the production of marked changes in the strength of bone. On the contrary, we have found fluctuations in breaking strength of as much as 40 per cent occurring in the short space of six days.<sup>3</sup>

In recent publications we have given the results of our determinations of the breaking strength of normal fibulae, as well as the healing strength of fractured fibulae, of rats fed various synthetic diets in which the salts had been adequately supplied.<sup>3</sup> Having found such remarkable changes in fibular strength in the animals on these diets, it became evident that fluctuations of at least equal degree should appear when the

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From the Department of Surgery, Yale University School of Medicine.

The expenses of this investigation were defrayed by Davis and Geck, Inc.

1. Aub, J. C.: The Harvey Lectures, 1928-1929, Baltimore, Williams & Wilkins Company, 1930, p. 151. Jaffe, H. L., and Bodansky, A.: *J. Exper. Med.* **52**:669, 1930.

2. McKeown, R. M.; Lindsay, M. K.; Harvey, S. C., and Howes, E. L.: The Breaking Strength of Healing Fractured Fibulae of Rats: II. Observations on a Standard Diet, *Arch. Surg.* **24**:458 (March) 1932.

3. McKeown, R. M.; Lindsay, M. K.; Harvey, S. C., and Howes, E. L.: The Breaking Strength of Healing Fractured Fibulae of Rats: II. Observations on a Standard Diet, *Arch. Surg.* **24**:458 (March) 1932; III. Observations on a High Fat Diet, *ibid.* **25**:467 (Sept.) 1932; IV. Observations on a High Carbohydrate Diet, *ibid.* **25**:749 (Oct.) 1932.

salts of the diet were varied. Particularly did we expect this to be the case when the calcium and phosphorus were above or below the normal requirements. The results of a low phosphorus diet will be reported later,<sup>4</sup> while in our present paper we shall discuss the influence exerted on the breaking strength of normal, and the healing strength of fractured, fibulae of rats on a low calcium diet.

The literature on the metabolism of calcium is so abundant that any attempt to present a detailed review of it would, for the time being at least, lead us too far afield. Suffice to say that a lowered calcium intake or an incomplete utilization of available calcium has been considered as being responsible for rickets,<sup>5</sup> osteomalacia,<sup>6</sup> achondroplasia,<sup>7</sup> osteogenesis imperfecta<sup>8</sup> and other diseases of the skeletal system. In the healing of fractures calcium is held to be of fundamental value,<sup>9</sup> and by some is even held to be, in certain cases, the causative agent of retarded healing.<sup>10</sup> Among the many theories concerning the growth and development of bone, calcium holds an equal place with phosphorus,<sup>11</sup> while its relationship to the metabolism of the parathyroid has been of particular interest to many investigators in recent years.<sup>12</sup>

#### EXPERIMENTATION

Albino rats aged from 6 to 8 months and weighing from 190 to 300 Gm. were selected for study. The diet used was identical with the standard Moise and Smith<sup>13</sup> diet previously reported,<sup>2</sup> except that the normal Osborne and Mendel<sup>15</sup> salt mixture included in the former diet was varied in such a manner that it contained no calcium. The changes made in the salt mixture were those undertaken by Osborne and

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7. Symmers, D., and Wallace, G. H.: Observations on the Pathological Changes in the Thyroid in a Cretinistic Variety of Chondrodystrophia Foetalis, *Arch. Int. Med.* **12**:37 (July) 1913.

8. Bolton, G. C.: *Deutsche Ztschr. f. Nervenhe.* **63**:343, 1919.

9. Barilli, A.: *J. de pharm. et chim.* **19**:14, 71, 196, 245 and 295, 1904.

10. Ravdin, I. S., and Jones, L.: *Ann. Surg.* **84**:37, 1926. Holt, L. E.; La Mer, V. K., and Chown, H. B.: *J. Biol. Chem.* **64**:509, 1925.

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12. Salvesen, H. A.: *J. Biol. Chem.* **56**:443, 1923. Collip, J. B.; Clark, E. P., and Scott, J. W.: *J. Biol. Chem.* **63**:439, 1925. Iselin, H.: *Deutsche Ztschr. f. Chir.* **93**:494, 1908.

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Mendel<sup>16</sup> in a study of the inorganic elements in nutrition, and the resulting combination after balancing the different salts consisted of the following:

*Calcium-Free Salt Mixture*

	Gm.
CaCO <sub>3</sub> .....	0.00
MgCO <sub>3</sub> .....	2.42
Na <sub>2</sub> CO <sub>3</sub> .....	5.80
K <sub>2</sub> CO <sub>3</sub> .....	14.13
H <sub>2</sub> PO <sub>4</sub> .....	3.72
HCL .....	5.34
H <sub>2</sub> SO <sub>4</sub> .....	0.92
Citric Acid H <sub>2</sub> O .....	11.11
Ferric Citrate 1½ H <sub>2</sub> O .....	0.634
KI .....	0.002
MnSO <sub>4</sub> .....	0.0079
NaF .....	0.0248
K <sub>2</sub> Al <sub>2</sub> (SO <sub>4</sub> ) <sup>2</sup> .....	0.00245
Lactose .....	246.00

When the entire diet was ashed, it was found that it had a calcium content of 0.043 per cent and a phosphorus content of 0.309 per cent. Consequently, the diet was actually calcium-low, and not calcium-free. The ratio of calcium to phosphorus was 1:7.2, which was roughly 12 times the phosphorus ratio Mellanby and Killick<sup>17</sup> gave as the normal ratio of bone as established by McCollum, who found the normal ratio to be 1:0.67. Eden,<sup>18</sup> in his study of the healing of bone, reported a basic ratio of calcium and phosphorus for adult bone essentially the same as that given by McCollum. From the analysis of our diet we felt safe in assuming the ration to be relatively high in phosphorus and absolutely low in calcium. In view of our completed, but unpublished work with a low phosphorus diet<sup>4</sup> our present study on a low calcium ration should afford us the opportunity for a direct comparison between the two in relation to their respective effects on the healing strength of fractured fibulae in rats.

At the end of one week on the diet, the rats were divided into two groups. The first group consisted of those animals in which the right fibulae were fractured in the manner described earlier,<sup>14</sup> while the second group served to control the first, and was made up of rats entirely free from fractures. In each of the two groups there were fourteen time periods in which the determinations of the breaking and healing strength were made. These periods began on the sixth postoperative day, and continued at intervals of three days thereafter to the forty-fifth day.

16. Osborne, T. B., and Mendel, L. B.: J. Biol. Chem. **34**:131, 1918.

17. Mellanby, M., and Killick, E. M.: Biochem. J. **20**:903, 1926.

18. Eden, R.: München. med. Wchnschr. **71**:1160, 1924.

19. Footnote deleted by authors.



In each of the intervals observed the breaking strengths of five fractures of the fractured group and of four controls of the control group were determined. The fractured and unfractured fibulae of each animal were prepared as described before, and the method of recording the strengths was identical with that given in the former work.<sup>2</sup>

The correlations between the body weight of the rat and the length and strength of its fibulae were dispensed with in this paper. These have been sufficiently studied to show that a positive correlation exists in each case regardless of the diet, even though the correlations are not so complete on some diets as on others.<sup>3</sup> Relative studies of the animal weights, the quantity of food they consumed and the roentgenographic appearance of their calluses were prepared as they had been before.<sup>3</sup>

### RESULTS

*The Unfractured Control Group.*—1. The Breaking Strength of the Control Fibulae: It was again noted that the breaking strength ratios for the right and left fibulae were in comparatively close proximity throughout the duration of the experiment.

TABLE 1.—*Ratios of the Breaking Forces of the Right and Left Fibulae with the Standard Deviation of the Mean in the Control Group on a Low Calcium Diet\**

Postoperative Days	Right Fibula	Left Fibula
6.....	345 $\pm$ 28	379 $\pm$ 39
9.....	231 $\pm$ 17	255 $\pm$ 23
12.....	291 $\pm$ 41	267 $\pm$ 37
15.....	338 $\pm$ 53	335 $\pm$ 58
18.....	274 $\pm$ 54	282 $\pm$ 56
21.....	238 $\pm$ 10	246 $\pm$ 16
24.....	316 $\pm$ 29	312 $\pm$ 37
27.....	292 $\pm$ 8	283 $\pm$ 10
30.....	321 $\pm$ 34	272 $\pm$ 25
33.....	206 $\pm$ 10	208 $\pm$ 20
36.....	199 $\pm$ 21	205 $\pm$ 17
39.....	239 $\pm$ 27	265 $\pm$ 29
42.....	254 $\pm$ 14	232 $\pm$ 18
45.....	195 $\pm$ 21	199 $\pm$ 22

\* Refer to table 1a for complete data.

On the sixth day of the experiment the ratios were 345 for the right and 379 for the left fibulae. By the ninth day the ratios had fallen to 231 for the right and 255 for the left. A sharp rise to a peak followed on the fifteenth day, at which time the ratios were 338 for the right and 335 for the left. Subsequently, fibular strength was lost as rapidly as it previously had been gained, until on the twenty-first day the ratio for the right was 238, and for the left it was 246. Thereafter, a rise occurred on the twenty-fourth day, a slight fall on the twenty-seventh day and a rapid drop on the thirty-third day (table 1). When the results were plotted it was observed that the fibulae made

another attempt to regain their original strength on the thirty-ninth and forty-second days, but despite this the strength remained below the normal band when the experiment was concluded on the forty-fifth day (fig. 1).

It was not until the thirty-third day had been reached that the strength of the control fibulae could be said to have become definitely less than normal. Thereafter, the curve of the fibular breaking strengths showed the characteristics manifested in the curves for the controls on both the standard<sup>14</sup> and the low phosphorus diet,<sup>19</sup> namely, a persistent but unsuccessful attempt to restore the strength that had been lost earlier. Prior to the thirty-third day, the strength of the fibulae of the

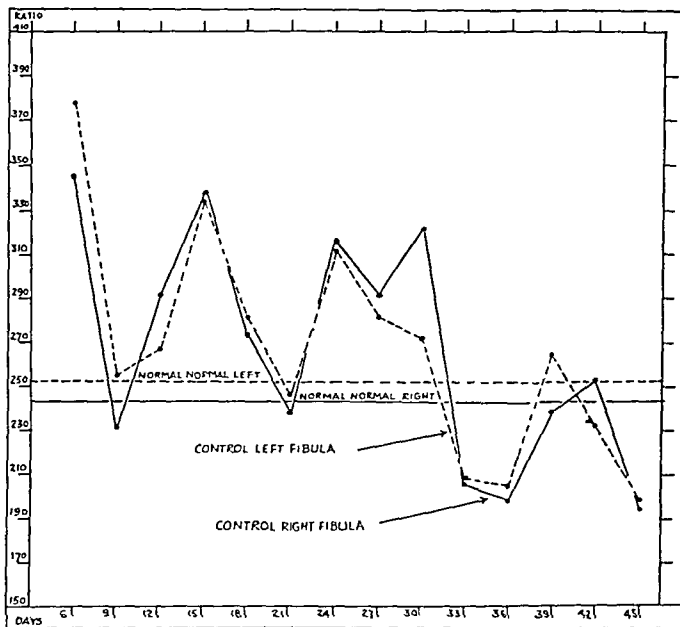


Fig. 1.—The breaking strength ratio of the left and the right fibula. The fibulae of the control rats on a low calcium diet maintained their strength more successfully than those of the controls on the standard or the low phosphorus diet. The normal band represents the breaking strength ratio of fifty pairs of normal rat fibulae.

control rats on a low calcium diet were more completely maintained than they had been in the rats on either the standard or the low phosphorus diet. Of the latter, the strength of the fibulae of the controls on a low phosphorus diet more closely approximated that of the controls on a low calcium diet than did the strength of the fibulae of the controls on the standard diet.

2. The Body Weights of the Control Rats and the Quantity of Food Consumed by Them: The body weights of the control rats diminished constantly, except for a momentary rise above their original weights on the twelfth day. An extremely sharp reduction in their body weights

took place on the eighteenth day, after which the weights fluctuated widely throughout the duration of the observations (table 2).

The body weights of the controls on this diet were greater than they had been in the case of the controls on the standard diet until the eighteenth day was reached. Later, although they at times equalled those of the controls on the standard diet, their average remained less. When the weights of these two control groups were graphed, it was found that the weights of the controls on a low calcium diet diverged from those of the controls on the standard diet on the twenty-first day more widely than they did before or after. Except for this particular day, the weights of the two control groups were not far apart (fig. 2).

TABLE 2.—*Body Weights and Quantities of Food Consumed in the Control Group on a Low Calcium Diet\**

Post-operative Days	Difference in Weight from Operation to Death as Percentage of Weight at Operation	Food Consumed per Day from Operation to Death as Percentage of Weight at Operation
6.....	— 1.2	3.0
9.....	— 2.7	3.2
12.....	+ 0.4	3.4
15.....	— 1.4	2.7
18.....	— 4.6	2.9
21.....	—21.2	2.7
24.....	— 7.7	3.8
27.....	—15.9	3.8
30.....	—10.7	2.6
33.....	—10.0	3.3
36.....	—14.0	3.9
39.....	— 4.9	5.8
42.....	—17.0	3.3
45.....	—17.6	3.4

\* Refer to tables 2a and 2b for complete data.

It was also found in the low phosphorus study that but for the interval between the thirtieth and forty-second days the weights of the controls on a low phosphorus diet were greater than those of the controls on the standard diet, and that the two groups were essentially of the same weight on the final or forty-fifth day.<sup>4</sup> It would appear, then, that on the last day of the experiment the weights of the controls on a low calcium diet were slightly greater than those of the controls on either the standard or the low phosphorus diet (fig. 2).

The quantity of the ration consumed by the controls on a low calcium diet was nearly equal to that consumed by the controls on the standard diet until the twelfth day. From then to the twenty-fourth day it was appreciably less, but subsequently it became greater. For purposes of comparison the amounts of the low calcium, the low phosphorus and the standard diets ingested by the different control groups have been charted (fig. 3). The graph shows that but little difference existed in the amounts of the respective rations taken by the rats until the twelfth day was reached. At that time the controls on a low phos-

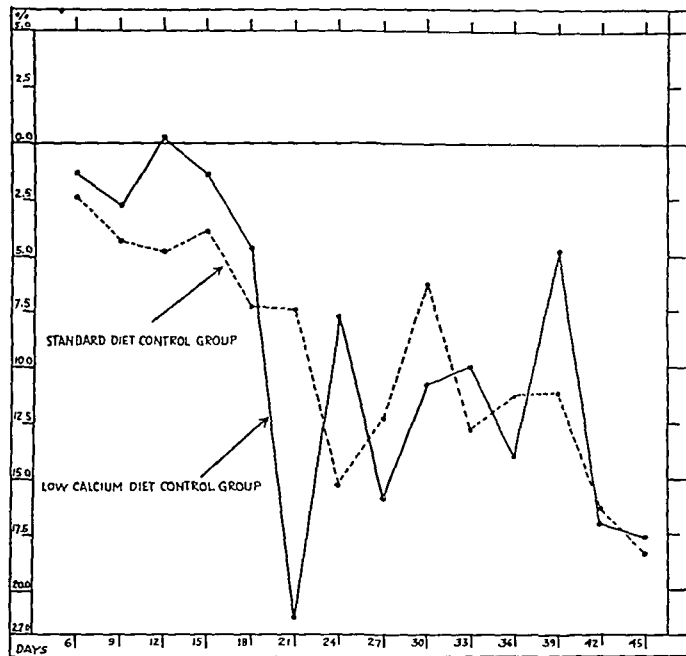


Fig. 2.—The difference in body weight from operation to death plotted as the percentage of body weight at operation of the control groups on the low calcium and standard diets. The weights of the controls on a low calcium diet were about the same as those of the controls on the standard diet. In both cases weight was lost throughout the course of the experiment. The early gain in weight of the controls on a low calcium diet was evidently due to an increased consumption of food.

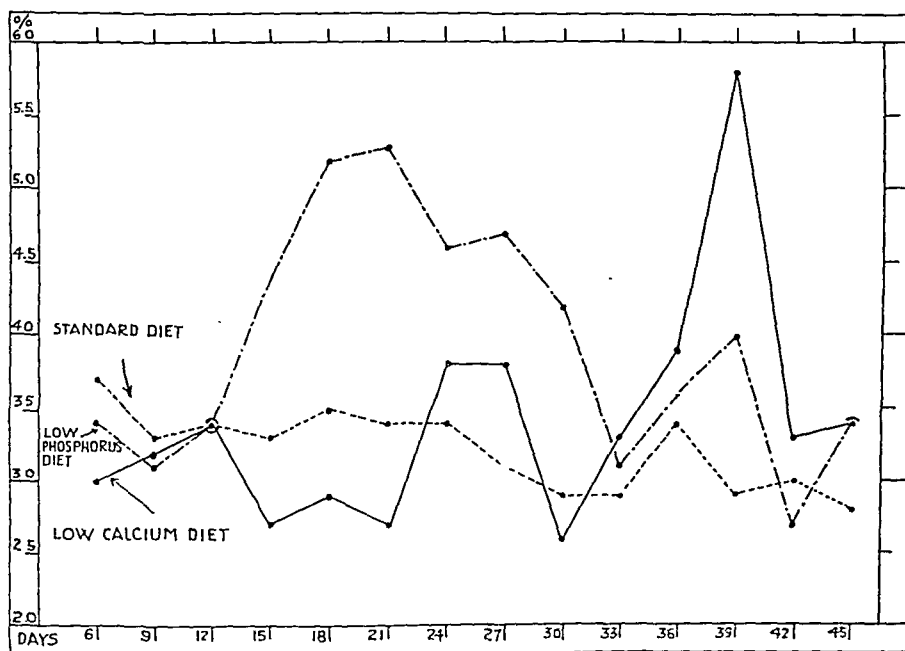


Fig. 3.—The quantity of food consumed per day from operation to death by the control rats on the low calcium, low phosphorus and standard diets, plotted as the percentage of body weight at operation. All three control groups ate about the same quantity of their ration for the first twelve days. Later they differed widely. Apparently, the deficiency in phosphorus led to a greater food intake than did a reduction in the calcium of the diet. After the thirty-third day, however, the reverse was true. Evidently a diminution in the phosphorus in the diet is felt earlier than is one of calcium. Subsequently, the calcium stores being depleted, an attempt is also made to overcome its deficiency in the ration by a greater food intake.

phorus diet consumed more food than either of the other two control groups, and those on the standard diet an amount intermediate between the relatively small amount taken by those on a low calcium diet and the greater quantity consumed by the rats on a low phosphorus diet. This remained comparatively constant until the thirty-third day, at which time the controls on a low calcium diet ate the greatest amount of their ration; the controls on the standard diet ate the least, and the controls on a low phosphorus diet consumed an intermediary amount of their food. This relationship of the amount of the respective diets eaten by

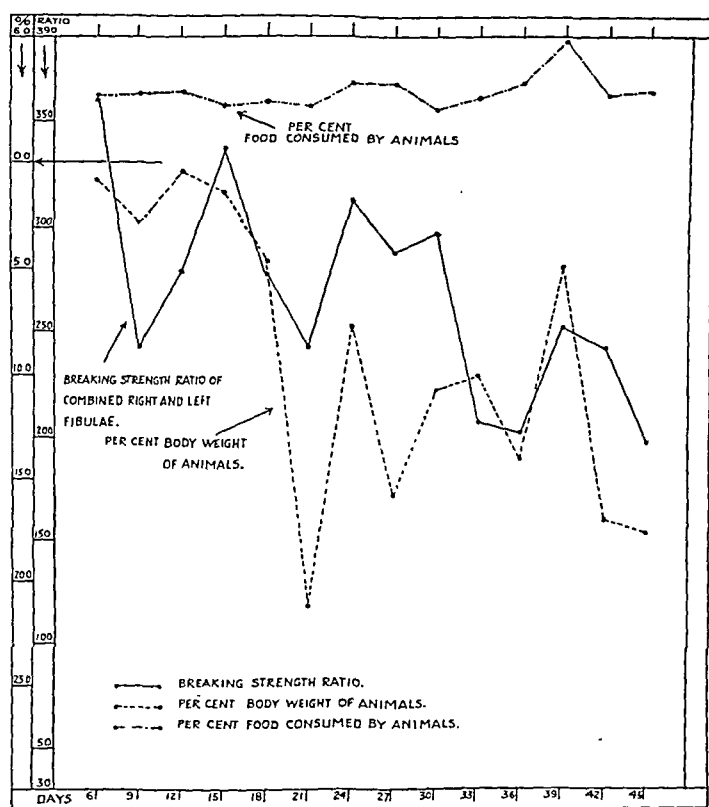


Fig. 4.—The metabolic correlation existing between the body weight, food consumption, and fibular breaking strength in the control group on a low calcium diet. As the weight is reduced the fibula grows weaker. Strength is temporarily restored to the bone when the food intake and body weights increase.

the different control groups persisted until the forty-fifth day was reached, when the controls on the low calcium and those on the low phosphorus diet ate about the same amounts, and the controls on the standard diet ate the least (fig. 3).

We have repeatedly stated that a correlation exists between the strength of the rat's fibula, its body weight and the quantity of food it consumes. For the first time we have plotted the curves for these three factors on the same chart, and it is observed that although the correlation present was only partial, it nevertheless existed (fig. 4).

A particularly clearcut relationship appeared to be evident between the curve for the animal weight and that for the fibular strength. The quantity of food consumed by the rats did not show the wide excursions in its plotted curve that the curve of the body weights and fibular strength did. However, variations do occur in the curve of food consumption simultaneously with similar variations in the weight and the fibular strength. It would appear that as the weight of the rat and the strength of its fibula diminished, the animal ate more of its ration in an attempt to offset the deficiencies of the diet. Such a condition is especially noticeable after the thirtieth day. We have already observed that the increased quantity of the low calcium diet taken by the control rats was followed by a more complete maintenance not only of body

TABLE 3.—*Ratios of the Breaking Forces of the Fractured Right and the Unfractured Left Fibulae with Their Standard Deviation of the Mean in the Fractured Group on a Low Calcium Diet \**

Postoperative Days	Fractured Right	Unfractured Left
6.....	1 $\pm$ 1	237 $\pm$ 16
9.....	84 $\pm$ 13	336 $\pm$ 23
12.....	99 $\pm$ 20	235 $\pm$ 38
15.....	122 $\pm$ 24	352 $\pm$ 25
18.....	233 $\pm$ 29	273 $\pm$ 37
21.....	148 $\pm$ 15	246 $\pm$ 9
24.....	133 $\pm$ 15	325 $\pm$ 33
27.....	124 $\pm$ 21	248 $\pm$ 18
30.....	151 $\pm$ 20	303 $\pm$ 25
33.....	166 $\pm$ 17	235 $\pm$ 30
36.....	209 $\pm$ 29	238 $\pm$ 24
39.....	224 $\pm$ 42	300 $\pm$ 43
42.....	185 $\pm$ 24	243 $\pm$ 20
45.....	138 $\pm$ 13	155 $\pm$ 19

\* Refer to table 3a for complete data.

weight but of fibular strength than it was in the controls on either the standard or the low phosphorus diet.

*The Fractured Group on a Low Calcium Diet.*—1. The Breaking Strength Ratio of the Fractured Right Fibula: The breaking, or healing, strength of the fractured right fibula showed a comparatively uniform increase from the sixth to the eighteenth postoperative days, when a ratio of 233 was observed. No tendency to reach a peak before the eighteenth day was found. This was not in accord with our earlier results on the standard, high fat and high carbohydrate diets, in which the first peak in the curve of healing strength was noted on the fifteenth day. It was felt from the findings on the later diets that the primary callus under theoretically normal conditions reaches its greatest strength on the fifteenth day; consequently, it was three days late in appearing on the low calcium diet. It will be shown subsequently that the peak was also three days late on the low phosphorus diet, and it would seem that

these two salt-deficient diets retard the formation of the provisional callus as much, if not more, as any diets we have studied previously.

After the eighteenth day peak the ratio fell on the twenty-seventh day to 124. Such a secondary fall taking place after a primary raise has been found to characterize all our diets with the exception of the high carbohydrate. By the thirty-ninth day the ratio had once more increased and was 209. However, by the conclusion of the experiment on the forty-fifth day, the ratio was down to 138, which was within a few points of the ratio noted earlier on the twenty-seventh day (table 3 and fig. 5).

2. The Breaking Strength Ratio of the Unfractured Left Fibula: The ratios observed for the unfractured left fibula showed little uni-

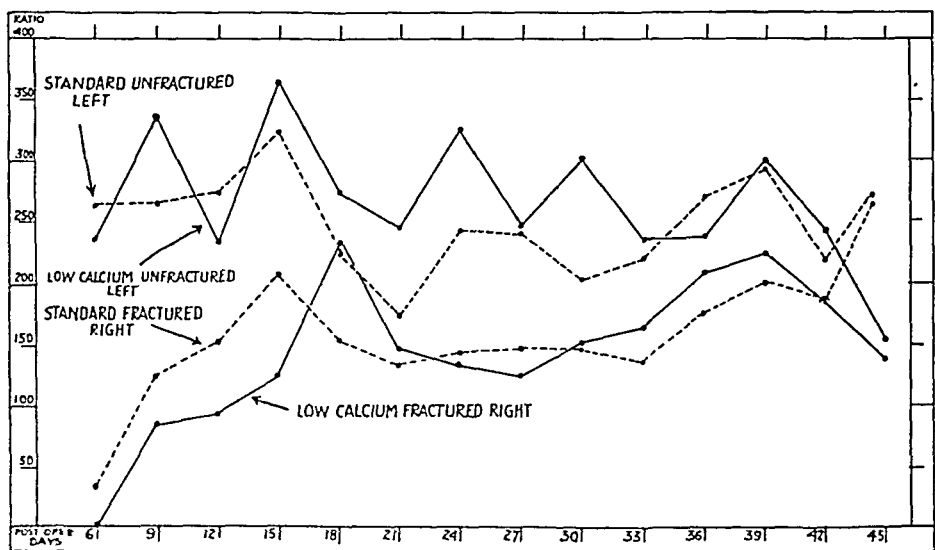


Fig. 5.—The breaking strength ratios of the fracture groups on the low calcium and standard diets. The primary callus was apparently not formed by the healing fractured right fibula on the low calcium diet until the eighteenth day, or three days later than it developed on the standard diet. Strength thereafter was lost as the medullary cavity developed. This was also observed earlier on the standard diet. The end-point on the forty-fifth day was lower than normal, but was within the normal time limits. The unfractured left fibula in the rats on the low calcium diet first gained strength in recognition of the generalized skeletal response to the fracture. Subsequently it lost strength as the deficiencies of the diet compelled it to furnish healing materials for the fracture.

formity, but on the contrary varied widely (fig. 5). The tabulated ratios indicate that the trend of fibular strength in these fibulae was constantly diminishing (table 3). In the graphed results it may be seen that the unfractured left fibulae of the rats on the standard diet varied directly as did the fractured right fibulae of the opposite legs (fig. 5). The statement was made in the report on the standard diet

that such agreement between the strengths of the two bones was produced by a generalized skeletal response to the presence of a fracture in the right fibula. In the curve for the ratios of the left fibulae of rats on the low calcium diet plotted on the same chart, no such clearcut similarity between the curves of the right and left fibulae was found (fig. 5). However, there is a resemblance between the two sufficiently close to indicate that in the first phase of the healing process the reparative action is generalized, resulting in an increase in the strength of the fracture and skeleton at large, while later, although it is still generalized in type, it is characterized by a loss in strength at points other than the fracture itself. The extent to which strength is lost elsewhere indicates the response of the fracture to the diet equally as well as strength

TABLE 4.—*Body Weight and Quantity of Food Consumed in the Fractured Group on a Low Calcium Diet \**

Post-operative Days	Difference in Weight from Operation to Death as Percentage of Weight at Operation	Food Consumed per Day from Operation to Death as Percentage of Weight at Operation
6.....	- 1.4	2.8
9.....	- 2.0	3.7
12.....	- 1.0	3.5
15.....	- 2.4	2.9
18.....	- 8.7	2.7
21.....	-10.0	3.5
24.....	- 6.0	3.9
27.....	- 5.2	2.9
30.....	-11.1	2.6
33.....	-12.9	3.4
36.....	-13.7	3.1
39.....	- 9.7	3.1
42.....	-14.5	3.2
45.....	-12.0	3.7

\* Refer to tables 4a and 4b for complete data.

variations in the fracture itself do. From the curve for the unfractured left fibulae of rats on the low calcium diet it is evident that less strength was lost by the left fibula on this diet, except for the forty-fifth day, than was lost by the left on the standard diet. Further, less strength was lost by the unfractured left fibulae of rats on the low calcium diet than was lost by the left fibulae of rats on the low phosphorus diet. The explanation of this we do not know, but it is not to be forgotten that the low calcium diet was relatively high in phosphorus despite its lowered calcium content.

2. The Body Weights and Food Consumption of the Fractured Group: There was a steady and relatively uniform diminution in the body weights over the course of the study (table 4). It was noted when the results were graphed that there was a slight increase in body weight during the first twelve days after operation (fig. 6). Such a primary gain had already been seen in the rats on the standard diet,



and was believed due to the increased metabolism following fracture. Unlike the rats on the standard diet, however, no successful effort was made at any time by these animals to regain their original weight.

It would naturally be expected, since the weights varied so slightly, that the amount of the ration consumed by the rats would also not fluctuate markedly. This proved true when the quantity of food ingested was tabulated (table 4). It was noted, too, when the plotted results were compared with similar results obtained in rats on the standard diet, that the food consumption of the fractured group on a low calcium diet was relatively more uniform than it was in the fractured rats

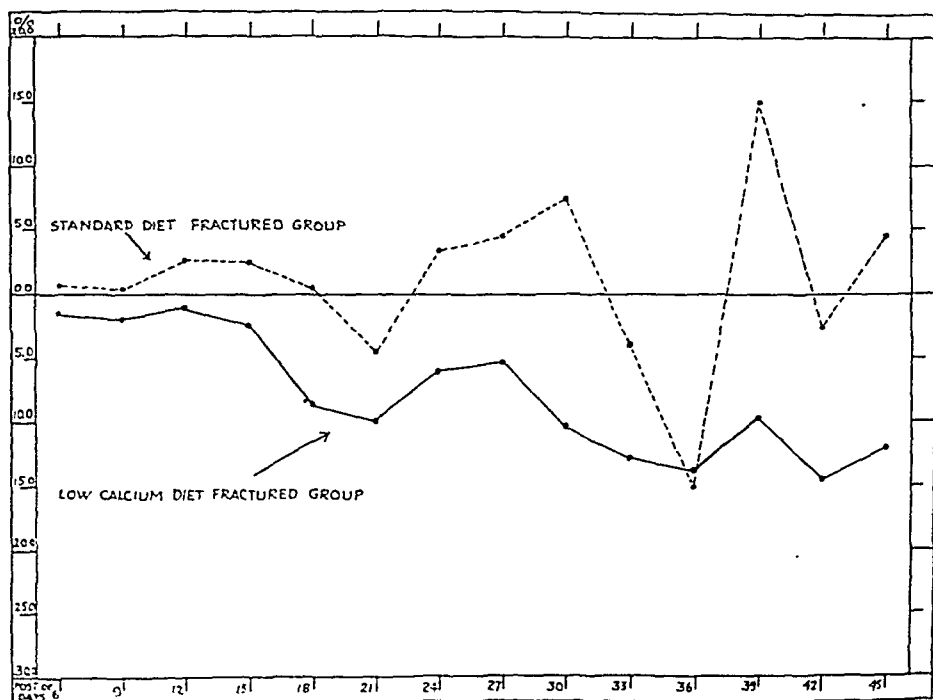


Fig. 6.—The difference in body weight from operation to death, plotted as the percentage of body weight at operation for the rats with fractured fibulae on the low calcium and standard diets. The fractured rats on a low calcium diet lost weight from the onset of the experiment. A moderate gain in the weight previously lost was noted from the ninth to the twelfth days. This may have been due to the increased metabolism in response to the repair of the fracture.

on the standard diet (fig. 7). In addition, when the curves of food intake for the low calcium and low phosphorus diets were compared, it was demonstrated that the animals on a low phosphorus diet varied much more in the amount of food they took than did those on a low calcium diet (fig. 7).

During the first eighteen days throughout which the primary callus was forming, we found the rats eating most of their ration on the ninth and twelfth days, and the least on the eighteenth day. Later

the food intake became greater, reaching its highest peak on the twenty-fourth day. During the time interval from eighteen to twenty-four days the strength of the healing fracture rapidly diminished as the callus was modeling out for the medullary space, yet we have seen that the food taken during this period of diminishing callus strength was greater than at any time before or after. It may be necessary to go back earlier than the eighteenth day to explain the reason for such a condition. It would seem that following the original impetus for an increased food intake, as was shown on the sixth to the twelfth days, the callus was sufficiently supplied by the diet and skeleton at large to permit of its healing at a slightly slower rate than normally. However, on, or close to, the eighteenth day, the process of decalcification of the

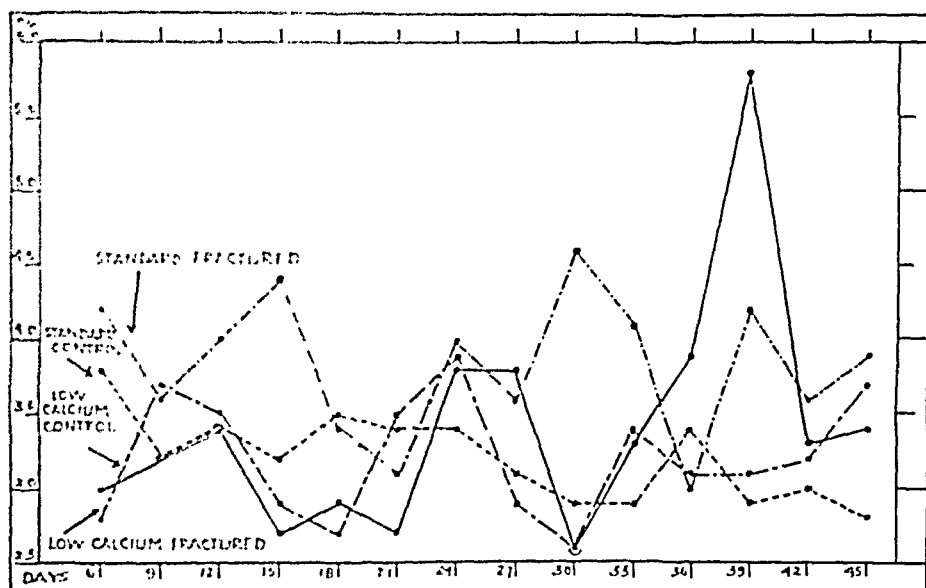


Fig. 7.—Quantity of low calcium and standard diets consumed per day by control and fractured groups, plotted as percentage of body weight at operation. For the first nine days the fractured rats on a low calcium diet showed an increase in the quantity of food they consumed. During that time they ate more of their ration than did their controls (represented by the solid line). This may have been due to the presence of the fracture, resulting in an increase in the metabolic rate. Later the two groups ate essentially the same amount until the thirty-ninth day when the controls ate considerably more.

callus assisting in the formation of the medullary space initiated some metabolic state of such a nature that it was followed by an increase in the amount of food consumed by the rats. The increase apparently did not exert much influence on the healing strength of the callus, but it did permit the left fibula to restore a large share of its lost strength. The diet alone was not, however, sufficient to supply the demands of the fracture for healing material, and the strength of the left fibula varied accordingly.

3. Roentgenographic Studies of Representative Fractures: The calcific process was delayed throughout the entire course of the experiment. In fact, the shadows for all the calluses are definitely lighter than normal. The callus on the eighteenth day shows a moderately strong side to side union, and it was on this day that our breaking strengths indicated the completion of primary callus formation. The

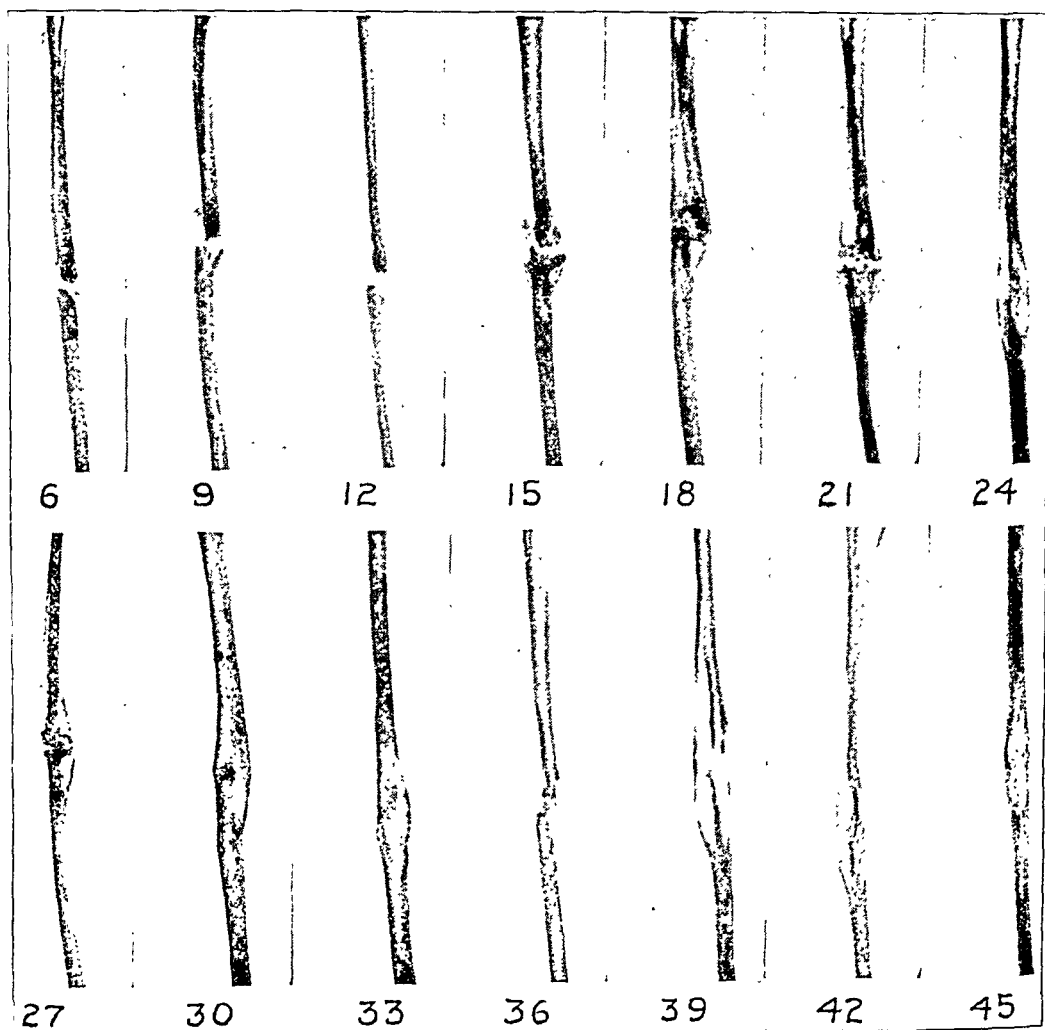


Fig. 8.—Roentgenograms of typical calluses at different postoperative days in the fractured group on a low calcium diet. The primary callus was apparently not formed until the eighteenth day, or three days later than on the standard diet. The resorption and rarefaction of the fragments are suggested throughout, especially so between the thirty-sixth and forty-second days. The thirty and thirty-third day fractures shown are obviously not representative. The fracture was evidently healed by the forty-fifth day, but with a callus possessing a minimum of inorganic salts. (Magnification  $\times 3\frac{1}{2}$ .)

resorption of the callus medially to develop the medullary space is suggested between the twenty-first and twenty-seventh days. The callus on the thirtieth day was not well selected for our purpose here, nor

was the thirty-third day fracture. However, subsequent calluses illustrate the gradual decalcification of the diaphysis and the eventual appearance of a well knit, although somewhat porous, callus on the forty-fifth postoperative day (fig. 8).

The x-ray pictures show fairly clearly the retardation in the deposition of calcium in the callus. Histologic studies of the representative fractures in rats on this diet also indicate a definite slowing up in the entire process of repair.<sup>20</sup> There was, however, considerable evidence in the histologic preparations that the strength found in these fractures, in spite of their lessened calcium content, was due to the increase, or more correctly the persistence, of the organic cellular matrix. Such being the case, it was not surprising that these fractures possessed more elasticity than the fractures of rats on the standard diet.

#### COMMENT

Rössle,<sup>21</sup> in an interesting study on the hardness of human bone, stated that in youth the bones are comparatively soft, while in the aged they are very hard. In a chemical analysis of the bones of rats, Hammett<sup>22</sup> showed that at 23 days of age the humeri had 35.93 per cent of calcium and 18.98 per cent of phosphorus, and at 150 days of age the calcium rose to 37.5 per cent and the phosphorus fell to 18.51 per cent. It would appear, then, and in fact has long been recognized, that the hardness of bone is directly proportional to its calcium content. There still remains, however, another factor in the strength of bone to be considered.

The strength of bone depends on its organic as well as on its inorganic constituents. The bones of youth contain more organic material than do those of the adult. Consequently, they possess not rigidity, but rather pliability or elasticity to a greater extent than do those of the older persons. Hammarsten and Hedin<sup>23</sup> expressed the opinion that the organic material of bone is primarily ossein, mucoid and albuminoid, which, expressed histologically rather than chemically, would indicate that the organic material of bone lies principally in its cellular constituents. Hence, the pliable bones of youth are more cellular with a minimal amount of inorganic deposits throughout their cellular matrix than are those of adults.

20. Downs, W. G., Jr., and McKeown, R. M.: Histology of Healing Fractures on a Normal Diet, Arch. Surg., to be published.

21. Rössle, R.: Beitr. z. path. Anat. u. z. allg. Path. **77**:174, 1927.

22. Hammett, F. S.: J. Biol. Chem. **65**:693, 1925.

23. Hammarsten, O., and Hedin, S. G.: Textbook of Physiological Chemistry, translated by J. A. Mandel, ed. 7, New York, John Wiley & Sons, Inc., 1915, p. 551.

In studies shortly to be published on the histology of the fractures of rats on a low calcium diet by Downs and McKeown,<sup>24</sup> evidence will be offered that fractures of rats on this diet show a retardation in the calcific and an accentuation in the organic states. Fibroblasts and cartilage cells fill the picture, the fibroblasts probably predominating. Later a report will be made on the breaking strength of decalcified healing calluses of the fibulae of rats. Sufficient foundation work has already been done to demonstrate that following decalcification the diaphysis and its callus bend to a remarkable degree before they break. Possibly, then, the reason the breaking strengths of healing calluses in rats on a low calcium diet were in such close proximity to those of the fractures of rats on the standard or normal diet, despite the obviously lower calcium content, was due to an absolute increase in the organic elements of the bony shaft and callus. The added ability to bend before breaking that these calluses would thus possess would compensate for their reduced inorganic content. In the light of our present knowledge this seems worthy of consideration.

The value of phosphorus in the growth and repair of bone has been widely recognized through the work of Phemister<sup>25</sup> and many others in this field of research. The essential value of phosphorus in cellular metabolism has likewise been known for some time. Peters,<sup>26</sup> in studies on unicellular organisms, showed quite clearly the importance of this element to growth. The relative increase in the phosphorus offered the rats on the low calcium ration superficially would appear to explain the overgrowth of the cellular elements in the callus. However, opposed to such a view is the fact that phosphates are known to be of fundamental importance to the successful activity of phosphatase in the process of calcification, according to the opinions of Martland and Robison,<sup>27</sup> Kay<sup>28</sup> and Murray.<sup>29</sup> As calcium was absolutely decreased in the diet fed our rats, and since calcium and phosphorus tend to balance each other, we should expect eventually not an increase of the phosphorus on the low calcium diet, but rather a compensatory decrease. Theoretically, the result of such an equilibratory process would seem to be a weaker bone, which we have already found not to be the case.

Roentgenologically, there is little doubt but that calcification was retarded by the low calcium diet. As we have repeatedly mentioned, the organic constituents of the callus do not show themselves by the roentgenogram, but histologically we found the cellular reaction to be

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24. Downs, W. G., Jr., and McKeown, R. M.: Studies in preparation.

25. Phemister, D. B.: The Effect of Phosphorus on Growing, Normal and Diseased Bones, *J. A. M. A.* **70**:1737 (June 8) 1918.

26. Peters, R. A.: *J. Physiol.* **55**:1, 1921.

27. Martland, M., and Robison, R.: *Biochem. J.* **23**:237, 1929.

28. Kay, H. D.: *Brit. J. Exper. Path.* **7**:177, 1926.

29. Murray, C. R.: *Ann. Surg.* **43**:961, 1931; *Minnesota Med.* **13**:137, 1930.

increased in rats on this diet.<sup>20</sup> The rarefied callus seen by the x-rays would indicate a callus of but little strength, yet our determinations of the breaking strength showed the opposite to be the case. Decalcification, or dissolution of the approximating ends of the fracture, was readily observed throughout the reparative state in these fractures, and yet healing by calcification was unduly delayed. Such a finding seems to be the reverse of what Murray's<sup>29</sup> results would lead us to expect. Murray is of the belief that the repair of fractures is largely local in character, and that the principal amount of calcium comes from a local source as a result of autolysis of bony fragments and the ends of fractures, as well as from the adjacent soft tissue. Resorption took place in the fractures of rats on the low calcium diet possibly at an even greater rate than normally, and yet calcification was delayed.

Any attempt to explain the cause of the increase in the cellular reaction over that occurring normally on a standard diet, in healing fractures of rats on the low calcium diet, would lead us too far afield. However, there are a few points that probe one's speculative powers. Loeb<sup>30</sup> has shown that the nucleus is the seat of the most energetic oxidation in the cell. Fibroblasts such as we found predominating in our histologic studies of the fractures of rats on this diet are not considered by investigators to be highly differentiated cells. According to Robertson,<sup>31</sup> such cells were fixed at a time when the pericellular concentration of their autocatalyst was relatively low. In consequence of this, the initial store of the autocatalyst that they received at the moment of their last nuclear division was relatively small. The absolute reduction in the calcium and the relative increase in the phosphorus in the ration fed the rats with healing fractures would hardly influence this process one way or the other. The phosphorus essential for the oxidative reaction in the nuclei of the numbers of fibroblasts seen in the fractures of rats on a low calcium diet could have been derived from carbohydrates, according to Paton,<sup>32</sup> but whether it was or was not we have no means of knowing. The influence of the diet as a result of which fibroplasia was accelerated and calcification inhibited was probably concerned in part, at least, with the inability of the fibroblasts to differentiate in a normal manner. Chondroblasts were not particularly numerous until late, and we have already noted that the calcification of the cellular matrix was delayed. It is entirely possible, however, that phosphorus did play an important part in the state of affairs existing. A reduction in the calcium intake would be followed

30. Loeb, Jacques: *Artificial Parthenogenesis and Fertilization*, Chicago, University of Chicago Press, 1913.

31. Robertson, T. B.: *Chemical Basis of Growth and Senescence*, Philadelphia, J. B. Lippincott Company, 1923, p. 188.

32. Paton, D. N.: *J. Physiol.* **19**:167, 1896; **22**:352, 1898.

subsequently by a compensatory decrease in the phosphorus of the body, and it is prevalent knowledge, especially through the work of Tisdall and Harris,<sup>33</sup> Sherman and Pappenheimer<sup>34</sup> and others, that phosphorus is of as much, if not more, value to the healing of fractures than calcium.

### CONCLUSIONS

The normal breaking strength of unfractured fibulae of albino rats fed a low calcium diet was more completely maintained than it had been on a low phosphorus diet. In some respects it was even better maintained than it had been on a standard, or normal, diet.

The healing strength of fractured fibulae of rats on a low calcium diet was relatively close to that for similar animals on a standard diet. This was found, when histologic and roentgenographic examinations were made, probably to be due to an absolute increase in the organic elements of the callus as represented by the cellular elements of the union. The result of this was an accentuation of the pliability, or elasticity, of the healing callus over that of normal tissue and an exaggeration of the factor of bending before breaking when the determinations of the breaking strength were made on the testing machine.

From the results obtained in rats on the low calcium diet, as compared with those soon to be reported in rats on a low phosphorus diet, it would appear that phosphorus is of more importance to the strength of healing fractures than calcium.

### COMPLETE DATA FOR LOW CALCIUM DIET

TABLE 1a.—*Breaking Forces and Ratios with the Standard Deviation of the Mean in the Low Calcium Control Group*

Postoperative Days	Rat Number	Weight (W)		Force (F)		Ratio (R)	
		At Operation	(10.W) <sup>2/3</sup>	Left	Right	Left	Right
6.....	3474	300	208.0	985	760	474	365
	3475	252	185.2	810	750	437	405
	3427	210	164.0	505	415	308	253
	3428	220	169.1	500	605	296	358
Arithmetic mean and standard deviation of the mean.....						379 ± 39	345 ± 28
9.....	3414	235	176.8	320	340	181	192
	3415	228	173.2	435	360	251	208
	3416	220	169.1	490	475	290	281
	3417	218	168.1	500	405	297	241
						255 ± 23	231 ± 17
12.....	3403	280	198.6	775	835	390	420
	3404	290	203.4	515	575	253	283
	3405	215	166.6	380	440	228	264
	3406	190	153.4	300	300	196	196
						267 ± 37	291 ± 41

33. Tisdall, F. F., and Harris, R. I.: Calcium and Phosphorus Metabolism in Patients with Fractures, *J. A. M. A.* 79:884 (Sept. 9) 1922.

34. Sherman, H. C., and Pappenheimer, A. M.: *Proc. Soc. Exper. Biol. & Med.* 18:193, 1920-1921.

TABLE 1a.—*Breaking Forces and Ratios with the Standard Deviation of the Mean in the Low Calcium Control Group—Continued*

Postoperative Days	Rat Number	Weight (W)		Force (F)		Ratio (R)	
		At Oper- ation	(10.W) <sup>2/3</sup>	Left	Right	Left	Right
15.....	3392	200	153.8	490	465	309	293
	3393	195	156.1	330	340	211	218
	3394	220	169.1	500	565	296	334
	3395	240	179.3	940	905	524	505
						335 ± 58	338 ± 53
18.....	3374	300	208.0	980	955	471	459
	3375	216	167.1	320	345	192	206
	3376	205	161.4	350	305	217	189
	3377	220	169.1	420	395	248	240
						282 ± 56	274 ± 54
21.....	3364	240	179.3	490	400	273	223
	3365	210	164.0	375	420	229	256
	3366	208	162.9	460	420	232	258
	3367	210	164.0	330	350	201	213
						246 ± 16	238 ± 10
24.....	3310	242	180.3	525	650	291	361
	3311	250	184.2	420	425	228	231
	3312	235	176.8	525	520	297	294
	3313	265	191.5	825	720	431	376
						312 ± 37	316 ± 29
27.....	3299	190	153.4	475	480	310	313
	3300	233	175.8	475	525	270	299
	3301	240	179.3	525	500	293	279
	3302	216	167.1	430	460	237	275
						288 ± 10	292 ± 8
30.....	3238	196	156.6	505	580	322	370
	3239	203	162.9	510	580	313	356
	3240	285	201.0	510	705	254	351
	3241	277	197.2	395	405	200	205
						272 ± 25	321 ± 34
33.....	3222	215	166.6	265	340	159	204
	3223	192	154.5	325	310	210	200
	3224	210	164.0	320	295	195	180
	3225	218	168.1	450	400	267	238
						208 ± 20	206 ± 10
36.....	3176	226	172.2	430	225	250	131
	3177	190	153.4	235	300	153	196
	3180	216	167.1	350	400	210	245
	3183	280	198.6	410	440	206	222
						205 ± 17	199 ± 21
39.....	3096	196	156.6	380	305	243	195
	3097	190	153.4	300	290	196	189
	3098	236	177.3	465	440	262	248
	3099	278	197.7	705	640	357	323
						265 ± 29	239 ± 27
42.....	2907	210	164.0	420	400	256	244
	2908	236	177.3	305	400	172	226
	2909	252	185.2	480	555	259	300
	2910	195	156.1	375	385	240	247
						232 ± 18	254 ± 14
45.....	2925	220	169.1	325	380	192	225
	2926	195	156.1	265	240	170	154
	2927	195	156.1	260	240	166	154
	2928	278	197.7	530	485	268	245
						199 ± 22	195 ± 21
48.....	2890	193	153.0	345	250	223	151
	2891	256	187.1	310	340	165	182
	2892	234	176.2	385	340	219	192
	2894	190	153.4	235	240	153	157
						199 ± 16	178 ± 7
51.....	2878	292	204.3	425	375	203	184
	2879	195	156.1	290	315	186	202
	2880	219	168.6	475	520	232	268
	2881	238	178.3	455	550	255	292
						235 ± 19	234 ± 25



TABLE 2a.—*Body Weights and Quantities of Food Consumed in the Low Calcium Control Group*

Postoperative Days	Rat Number	Weight			Food Consumed	
		Start	Operation	Death	Start to Operation	Operation to Death
6.....	3474	290	300	292	76	46
	3475	248	252	238	64	44
	3427	190	210	212	57	40
	3428	190	220	230	80	51
Arithmetic mean.....	....	230	246	243	69	45
9.....	3414	210	235	226	79	63
	3415	200	228	220	84	64
	3416	190	220	218	80	71
	3417	195	218	210	76	64
		199	225	219	80	66
12.....	3403	270	280	290	68	122
	3404	265	290	280	92	98
	3405	190	215	220	77	85
	3406	190	190	190	54	88
		229	244	245	73	98
15.....	3392	200	200	200	60	80
	3393	192	195	194	60	106
	3394	210	220	220	55	94
	3395	235	240	230	50	69
		209	214	211	56	87
18.....	3374	300	300	300	90	164
	3375	208	216	208	73	118
	3376	210	218	200	58	102
	3377	212	220	205	73	113
		233	239	228	74	124
21.....	3364	240	240	168	64	103
	3365	198	210	173	45	103
	3366	200	208	180	58	158
	3367	197	210	164	69	125
		209	217	171	59	122
24.....	3310	220	242	238	54	232
	3311	226	250	230	60	239
	3312	210	235	212	56	170
	3313	240	265	235	70	261
		224	248	229	60	226
27.....	3290	200	190	173	32	113
	3300	220	233	176	67	236
	3301	220	240	195	94	344
	3302	230	216	195	52	219
		218	220	185	61	228
30.....	3238	202	196	170	47	210
	3239	190	208	210	62	196
	3240	290	285	240	59	193
	3241	282	277	245	53	162
		241	242	216	55	190
33.....	3222	204	215	208	66	237
	3223	200	192	160	50	236
	3224	210	210	186	50	196
	3225	240	218	198	30	221
		214	209	188	49	223
36.....	3176	200	226	195	67	272
	3177	190	190	160	42	238
	3180	190	216	180	67	476
	3183	260	280	250	56	294
		210	228	196	58	320
39.....	3096	195	196	170	74	580
	3097	190	190	180	35	569
	3098	265	236	230	45	431
	3099	292	278	275	77	453
		236	225	214	58	508

TABLE 2a.—*Body Weights and Quantities of Food Consumed in the Low Calcium Control Group—Continued*

Postoperative Days	Rat Number	Weight			Food Consumed	
		Start	Operation	Death	Start to Operation	Operation to Death
42.....	2907	190	210	176	55	418
	2908	232	236	218	41	324
	2909	248	252	150	56	208
	2910	215	195	195	39	277
		221	223	185	48	307
45.....	2925	245	220	200	50	302
	2926	190	195	150	49	363
	2927	200	195	160	52	316
	2928	290	278	220	74	368
		231	222	183	56	337
48.....	2890	195	193	175	52	277
	2891	255	256	210	54	349
	2892	230	234	210	66	449
	2894	200	190	140	73	396
		220	218	184	61	368
51.....	2878	278	292	252	91	530
	2879	201	195	164	55	551
	2880	234	219	148	50	365
	2881	237	238	198	67	455
		238	236	191	66	475

TABLE 2b.—*Summary of Body Weights and Quantities of Food Consumed in the Low Calcium Control Group*

Postoperative Days	Weight at Operation, Gm.	Difference in Weight from Operation to Death, Gm.	Food Consumed per Day from Operation to Death, Gm.	Difference in Weight from Operation to Death as Percentage of Weight at Operation	Food Consumed per Day from Operation to Death as Percentage of Weight at Operation
6	246	— 3	7.5	— 1.2	3.0
9	225	— 6	7.3	— 2.7	3.2
12	244	+ 1	8.2	+ 0.4	3.4
15	214	— 3	5.8	— 1.4	2.7
18	239	—11	6.9	— 4.6	2.9
21	217	—46	5.8	—21.2	2.7
24	248	—19	9.4	— 7.7	3.8
27	220	—35	8.4	—15.9	3.8
30	242	—26	6.3	—10.7	2.6
33	209	—21	6.8	—10.0	3.3
36	228	—32	8.9	—14.0	3.9
39	225	—11	13.0	— 4.9	5.8
42	223	—38	7.3	—17.0	3.3
45	222	—39	7.5	—17.6	3.4
48	218	—34	7.7	—15.6	3.5
51	236	—45	9.3	—19.1	3.9

TABLE 3a.—*Breaking Force and Its Ratio with Standard Deviation of the Mean in the Low Calcium Fractured Group*

Postoperative Days	Rat Number	Weight (W)		Force (F)		Ratio (R)	
		At Operation	(10.W) <sup>2/3</sup>	Left	Right	Left	Right
6.....	3421	210	164.0	340	0	207	0
	3422	236	177.3	460	0	252	0
	3423	206	161.9	480	0	296	0
	3424	234	176.2	370	0	210	0
	3426	205	161.4	340	5	211	5
Arithmetic mean and standard deviation of the mean.....						237 ± 16	1 ± 1
9.....	3811	215	166.6	650	105	290	63
	3812	190	153.4	610	195	298	127
	3813	199	153.4	590	95	326	61
	3814	205	161.4	470	175	241	165
	3815	212	165.0	450	160	278	61
						356 ± 25	84 ± 17

TABLE 3a.—*Breaking Force and Its Ratio with Standard Deviation of the Mean in the Low Calcium Fractured Group—Continued*

Postoperative Days	Rat Number	Weight (W)		Force (F)		Ratio (R)	
		At Oper- ation	(10.W) <sup>2/3</sup>	Left	Right	Left	Right
12.....	3397	206	161.9	240	240	148	148
	3398	196	156.6	535	175	342	112
	3400	196	156.6	415	75	265	48
	3402	214	166.1	305	100	184	60
						235 ± 38	92 ± 20
15.....	3805	215	166.6	710	175	426	105
	3806	200	158.8	430	...	271	...
	3807	200	158.8	535	300	337	189
	3809	210	164.0	540	95	329	58
	3910	210	164.0	655	225	399	137
						352 ± 25	122 ± 24
18.....	3653	192	154.5	530	330	343	214
	3654	250	184.2	480	445	261	242
	3655	252	185.2	290	325	157	175
	3656	200	158.8	610	560	384	353
	3657	200	158.8	350	290	220	183
						273 ± 37	233 ± 29
21.....	3358	200	158.8	400	260	252	164
	3359	205	161.4	390	215	242	133
	3360	206	161.9	440	150	272	93
	3362	240	179.3	450	345	251	192
	3363	200	158.8	340	250	214	157
						246 ± 9	148 ± 15
24.....	3293	254	186.2	740	270	397	145
	3303	240	179.3	470	200	262	112
	3304	265	191.5	675	375	352	196
	3305	300	208.0	820	230	394	111
	3306	270	193.9	425	200	219	103
						325 ± 33	133 ± 15
27.....	3292	230	174.2	530	135	304	77
	3295	206	156.6	320	100	204	64
	3296	204	155.6	400	275	257	177
	3298	268	192.9	410	250	213	130
	3307	255	186.7	490	325	262	174
						248 ± 18	124 ± 21
30.....	3231	276	196.8	635	275	323	140
	3232	265	191.5	420	295	219	154
	3233	275	196.3	540	205	275	104
	3236	284	200.6	765	255	381	127
	3237	250	184.2	585	425	318	231
						303 ± 25	151 ± 20
33.....	3216	200	158.8	245	280	154	180
	3218	263	190.5	550	440	288	231
	3219	234	176.2	440	255	250	145
	3220	224	171.2	460	260	269	152
	3221	198	157.7	340	190	216	120
						235 ± 30	166 ± 17
36.....	3250	190	153.4	380	300	248	196
	3252	198	157.7	450	205	286	130
	3253	272	194.9	540	460	277	236
	3255	264	191.0	260	320	136	168
	3256	206	161.9	390	510	241	315
						238 ± 24	209 ± 29
39.....	3089	190	153.4	405	245	264	160
	3090	234	176.2	425	150	241	85
	3091	192	154.5	415	440	268	285
	3094	267	192.5	940	670	488	348
	3249	198	157.7	375	380	238	241
						300 ± 43	224 ± 42
42.....	2201	224	171.2	490	360	286	210
	2202	282	199.6	590	315	296	158
	2205	212	165.0	405	400	245	242
	2206	200	158.8	285	150	179	94
	2248	222	170.2	355	375	209	220
						243 ± 20	185 ± 24
45.....	2220	195	156.1	360	240	231	154
	2220	190	153.4	200	145	130	95
	2231	220	169.1	225	200	133	119
	2232	225	171.7	195	300	114	175
	2233	230	184.2	305	275	166	149
						155 ± 19	138 ± 13

TABLE 4a.—*Body Weights and Quantities of Food Consumed in the Low Calcium Fractured Group*

Postoperative Days	Rat Number	Weight			Food Consumed		o
		Start	Operation	Death	Start to Operation	Operation to Death	
6.....	3421	200	210	215	58	45	
	3422	195	236	213	77	17	
	3423	190	206	202	68	36	
	3424	220	234	235	64	38	
	3426	190	205	210	62	42	
Arithmetic mean.....	....	199	218	215	66	36	
9.....	3811	208	215	210	61	77	
	3812	190	190	178	63	72	
	3813	205	190	202	24	67	
	3814	195	205	200	62	63	
	3815	212	212	200	60	65	
		202	202	198	54	69	
12.....	3396	230	238	230	70	80	
	3397	195	206	206	62	74	
	3398	205	196	200	48	70	
	3400	190	196	192	78	116	
	3402	210	214	210	65	95	
		206	210	208	65	87	
15.....	3805	210	215	220	53	100	
	3806	195	200	200	60	95	
	3807	193	200	190	48	83	
	3809	210	210	200	47	75	
	3810	212	210	200	52	85	
		204	207	202	52	88	
18.....	3653	200	192	170	44	62	
	3654	242	250	220	73	107	
	3655	235	252	210	82	171	
	3656	195	200	200	53	93	
	3657	190	200	200	51	100	
		212	219	200	61	107	
21.....	3358	194	200	196	64	159	
	3359	212	205	170	54	206	
	3360	205	206	182	55	165	
	3362	240	240	210	62	130	
	3363	208	200	186	54	120	
		212	210	189	58	156	
24.....	3293	243	254	228	67	185	
	3303	218	240	236	66	187	
	3304	234	265	240	76	254	
	3305	265	300	284	82	223	
	3306	232	270	264	75	243	
		233	266	250	73	252	
27.....	3292	208	230	194	72	172	
	3295	218	206	183	76	187	
	3296	192	204	198	48	152	
	3298	275	268	270	54	228	
	3307	240	255	262	51	182	
		227	233	221	60	184	
30.....	3231	270	276	210	58	170	
	3232	265	265	220	55	186	
	3233	278	275	220	64	191	
	3236	266	284	284	74	205	
	3237	248	250	265	52	208	
		265	270	240	61	210	
33.....	3216	202	200	192	66	240	
	3218	285	263	207	66	280	
	3219	246	254	210	66	218	
	3220	215	224	173	76	300	
	3221	200	198	192	64	224	
		209	224	195	66	254	
36.....	3250	190	190	190	64	252	
	3252	220	198	163	48	297	
	3253	276	272	210	64	277	
	3255	272	284	250	70	185	
	3256	205	206	210	85	226	
		222	226	195	66	242	

TABLE 4a.—*Body Weights and Quantities of Food Consumed in the Low Calcium Fractured Group—Continued*

Postoperative Days	Rat Number	Weight			Food Consumed	
		Start	Operation	Death	Start to Operation	Operation to Death
39.....	3089	193	190	175	42	202
	3090	230	234	200	74	417
	3091	198	192	188	50	229
	3094	270	267	250	72	291
	3249	196	198	164	69	184
		217	216	195	61	265
42.....	2901	220	224	185	70	301
	2902	290	282	226	47	292
	2905	216	212	202	60	303
	2906	196	200	173	57	346
	3248	220	222	188	60	281
		228	228	195	59	305
45.....	2929	205	195	180	52	229
	2930	195	190	160	55	439
	2931	230	220	190	53	322
	2932	210	225	186	73	454
	2933	242	250	232	67	365
		216	216	190	60	362

TABLE 4b.—*Summary of Body Weights and Quantities of Food Consumed in the Low Calcium Fractured Group*

Postoperative Days	Weight at Operation, Gm.	Difference in Weight from Operation to Death, Gm.	Food Consumed per Day from Operation to Death, Gm.	Difference in Weight from Operation to Death as Percentage of Weight at Operation	Food Consumed per Day from Operation to Death as Percentage of Weight at Operation
6	218	— 3	6.0	— 1.4	2.8
9	202	— 4	7.4	— 2.0	3.7
12	210	— 2	7.3	— 1.0	3.5
15	207	— 5	5.9	— 2.4	2.9
18	219	—19	5.0	— 8.7	2.7
21	210	—21	7.4	—10.0	3.5
24	266	—16	10.5	— 6.0	3.9
27	233	—12	6.8	— 5.2	2.9
30	270	—30	7.0	—11.1	2.6
33	224	—29	7.7	—12.9	3.4
36	226	—31	6.9	—13.7	3.1
39	216	—21	6.8	— 9.7	3.1
42	228	—33	7.3	—14.5	3.2
45	216	—26	8.0	—12.0	3.7
48	255	—21	7.0	— 8.2	2.7
51	199	—49	6.4	—24.6	3.2

# THE EFFECT OF VIOSTEROL ON THE PERIOSTEUM IN EXPERIMENTAL FRACTURES

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Numerous studies have been made in order to link osteogenesis and bony repair after fracture with calcium metabolism. Other studies have been concerned with attempts to explain nonunion after fracture on the basis of alteration in the serum calcium and phosphorus values. In the present work a detailed study of alterations in the calcium, inorganic phosphorus and protein values of the blood serum in experimental fractures was made through the administration of graded doses of viosterol.

The relationship of vitamin D to calcium metabolism has been generally accepted since the work of McCollum in 1922. With the advent of viosterol an opportunity was afforded to study this substance in its relationship to osteogenesis. The calcium salts are intimately bound up with bone formation in the fetus, with bone repair in the adult and with bony metaplasia. There is little wonder that the obvious association was seized on by numerous workers. Hellner<sup>1</sup> showed that the feeding of viosterol to rats and guinea-pigs did not influence callus formation in experimentally produced fractures. R. Vara-Lopez<sup>2</sup> confirmed these observations by roentgenologic studies. Swart, in this country, came to similar conclusions after a series of experiments on rats and rabbits. Bors<sup>3</sup> observed a change in callus formation in the treated animals on from the twelfth to the fifteenth day as compared with the normal control. The differences in the results obtained by these workers, together with an appreciation of the value of a detailed histologic study of the changes following the administration of viosterol, led me to conduct a series of experiments in order to evaluate properly the varied observations. The series included both chemical and histologic studies.

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From the William H. Singer Memorial Research Laboratory, the Allegheny General Hospital.

1. Hellner, H.: Der Einfluss des Vigantols auf den Frakturcallus beim gesunden Versuchstier, *Deutsche Ztschr. f. Chir.* **209**:307, 1928.

2. Vara-Lopez, R.: Effect of Vigantol on Bone Regeneration, *Deutsche Ztschr. f. Chir.* **212**:101, 1928.

3. Bors, E.: Vigantol und Frakturheilung, *Zentralbl. f. Chir.* **54**:3266 (Dec. 17) 1927.

## EXPERIMENTAL WORK

Guinea-pigs appear to be least subject to the toxic effects of viosterol,<sup>4</sup> and these were inadvertently selected for the experimental work. The animals employed were fully grown adults and were selected at random from the stock animals. They were fed on the ordinary laboratory diet, which consisted of leafy greens, bread and hay, during the entire course of the experiments. Their weights were recorded at the outset and again at later dates when the appearance of the animals indicated a loss in weight. Seven groups, each of which consisted of at least six guinea-pigs, were used. After various preliminary efforts to secure a fracture in which the least amount of displacement of the fragments resulted, the right radius was selected as the bone of choice. In the front leg, the ulna acted as an internal splint. The hind leg was less desirable because the propulsive force required in walking displaced the fragments. The fractures were all produced by open osteotomy under as aseptic conditions as possible. The wounds were closed by several layers of adhesive tape, and the animals were allowed to run around in the cages.

The guinea-pigs received daily doses as follows: 0.75, 1, 2, 5, 10 and 15 mg., respectively. One group of pigs was used as a control and received no viosterol. Two samples of the oil were used, which consisted of viosterol in corn oil, each standardized so that 1 cc. equaled 5 mg. During the small doses the oil was administered intramuscularly. As the amount employed was increased (from 10 to 15 mg.), it was found that the oil was not being absorbed and so the oral route was used. Smith and Elvove<sup>5</sup> noted that the mechanism of its action was unchanged whether it was given by mouth or intramuscularly.

One of each of the groups receiving a smaller dose and one control animal were killed after fourteen days. The animals given the larger (toxic) doses were killed from five to seven days after fracture. Subsequently an animal from each group was killed at seven day intervals up to the forty-second and the fiftieth day. The variations in the doses employed determined the length of time over which the animals were followed.

## ANALYSIS OF BLOOD DETERMINATIONS

All animals were bled from the heart previous to being killed, and determinations of inorganic phosphorus, serum protein and calcium were made. Since the variations in serum calcium can be interpreted

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4. Shohl, A. T.; Goldblatt, H., and Brown, Helen B.: The Pathological Effects Upon Rats of Excess Irradiated Ergosterol, *J. Clin. Investigation* **3**:505 (June 20) 1930.

5. Smith, Maurice I., and Elvove E.: Action of Irradiated Ergosterol in the Rabbit, *Pub. Health Rep.* **44**: (May 24) 1929.

accurately only when the protein and inorganic phosphorus are also determined,<sup>6</sup> it was decided to make these observations in all instances.

Table 1 shows the analyses of the blood serum in the control group of guinea-pigs and in those that received 0.75 mg. The averages were taken in each group for comparative purposes, and in this way the

TABLE 1.—*Analyses of the Blood Serum in the Control Group and in Guinea-Pigs Given 0.75 Mg. of Viosterol*

Number	Weight, Gm.	Sex	Dose, Mg.	Autopsy, Days	Calcium, Mg.	Phosphorus, Mg.	Protein, per Cent
144	315	F	Control	15	10.0	6.01	4.0
145	300	M	Control	21	10.5	3.17	4.7
147	305	F	Control	30	10.9	*	*
146	355	F	Control	36	11.2	4.88	4.6
137	335	F	Control	42	11.7	4.59	4.4
148	460	M	Control	50	11.4	4.46	5.6
Average.....					10.9	4.82	4.6
140	315	F	0.75	15	10.2	5.78	4.1
139	300	F	0.75	21	10.4	3.83	4.7
138	260	M	0.75	30	11.5	3.19	5.0
136	365	M	0.75	36	10.0	5.12	4.8
141	280	F	0.75	42	10.2	5.58	*
143	460	M	0.75	50	12.0	6.86	6.1
Average.....					10.7	5.06	4.9

\* Quantity insufficient.

TABLE 2.—*Analyses of the Blood Serum in Guinea-Pigs Given 1 and 2 Mg. of Viosterol*

Number	Weight, Gm.	Sex	Dose, Mg.	Autopsy, Days	Calcium, Mg.	Phosphorus, Mg.	Protein, per Cent
149	360	F	1	7	11.7	7.02	*
160	570	M	1	11	†	†	†
151	390	F	1	14	13.1	4.56	5.3
167	530	M	1	21	12.8	3.09	4.3
165	420	F	1	28	10.3	4.31	4.4
154	456	F	1	36	11.2	4.84	5.6
166	370	F	1	45	11.0	5.8	5.0
Average.....					11.6	4.93	4.9
150	375	F	2	7	10.8	7.16	4.4
157	380	F	2	14	10.0	4.00	5.4
155	510	F	2	21	12.1	4.03	5.0
163	460	F	2	28	13.0	3.43	5.4
159	460	F	2	36	11.8	5.78	*
152	460	F	2	45	10.0	6.38	7.5
158	480	F	2	45	10.5	6.51	*
Average.....					11.1	5.3	5.5

\* Quantity insufficient.

† Died of pneumonia.

normal control data for cases of fracture in the animals were established. A study of the blood in the control group with the progress of time revealed a gradual increase in the serum calcium without a proportionate increase in the phosphorus and protein. This is a condition that is frequently seen in cases of fracture in the human being under normal con-

6. Peters, John P., and Eiserson, Leo: The Influence of Protein and Inorganic Phosphorus on Serum Calcium. *J. Biol. Chem.* **84**:155, 1929.



ditions.<sup>7</sup> The averages of the group given 0.75 mg. show no great variations from the results in the control group, though prolonged administration (for fifty days) showed the greatest rise in one instance. When 1 mg. was administered daily (table 2) the calcium content rose about 10 per cent while the protein and phosphorus remained fairly constant. A proportionate increase in the phosphorus and protein content was seen in the averages of the group given 2 mg. This was maintained

TABLE 3.—*Analyses of the Blood Serum in Guinea-Pigs Given 5 and 10 Mg. of Viosterol*

Number	Weight, Gm.	Sex	Dose, Mg.	Autopsy, Days	Calcium, Mg.	Phosphorus, Mg.	Protein, per Cent
311	640	F	5	5	10.0	4.53	5.3
305	570	F	5	9	12.8	4.53	5.3
310	600	F	5	16	10.0	7.8	7.5
309	530	F	5	25	10.47	*	4.73
301	550	F	5	31	11.33	*	4.82
306	670	F	5	40	14.45	*	5.21
325	380	F	5	47	12.27	5.4	5.78
Average.....					11.61	5.56	5.52
303	675	F	10	5	10.9	4.19	5.0
302	610	F	10	9	11.8	6.72	4.6
315	495	F	10	16	10.6	6.95	5.5
321	565	F	10	25	10.6	*	6.3
319	525	F	10	31	12.43	*	6.4
304	720	F	10	40	13.8	*	4.9
323	550	F	10	47	11.8	6.9	5.3
Average.....					11.72	6.19	5.45

\* Quantity insufficient.

TABLE 4.—*Analysis of the Blood Serum in Guinea-Pigs Given 15 Mg. of Viosterol*

Number	Weight, Gm.	Sex	Dose, Mg.	Autopsy, Days	Calcium, Mg.	Phosphorus, Mg.	Protein, per Cent
158	510	F	15	5	10.6	5.6	5.0
19	525	F	15	9	13.3	*	*
137	555	F	15	16	11.0	5.0	5.4
178	540	F	15	19	12.0	*	*
70	485	F	15	25	Found dead		
2	610	F	15	36	12.6	5.3	5.7
Average.....					11.9	5.3	5.36

\* Quantity insufficient.

throughout in the higher doses, as seen in tables 3 and 4. Practically all the tables show a primary rise in the early days of administration of the viosterol, the reaching of a maximum increase and then a gradual fall in the content of the serum calcium in many instances.

As the doses were increased to 15 mg., toxic manifestations became apparent. These consisted of anorexia and loss of weight, accompanied by listlessness and weakness. No gastro-intestinal disturbances were apparent. After nine days, a loss of 115 Gm. was present in guinea-

7. Kugelmass, I. N., and Berg, R. N.: Ossification: I. Callus Formation and Calcification, *Am. J. Dis. Child.* **41**:236 (Feb.) 1931.

pig 158. A loss of 215 Gm. was seen after nineteen days (when the animal was moribund) in guinea-pig 178. No. 70 was found dead on the twenty-fifth day and had lost 230 Gm. in weight. These observations only tend to emphasize the wide range in dosage that may be employed before outward toxic manifestations are apparent. Determination of the serum calcium alone will not give an adequate conception of the amount of damage to tissues with large doses.

The primary rise and subsequent fall in the serum values are in accord with the observations of Reed and Thacker,<sup>8</sup> who concluded that a certain tolerance was acquired by their experimental animals with long-continued therapeutic doses. In the accompanying results the same phenomenon is noted, apparently, even with the higher doses. Certain isolated discrepancies can be noted, such as a fall of the phosphorus level from the average normal, or an undue rise, which I can account for only by the fact that the experimental animals were not kept on a basal vitamin-free diet, but were given the ordinary laboratory ration. In this manner individual variations in the calcium and phosphorus intake occurred which were reflected in the serum determinations.

#### HISTOLOGIC STUDIES

The fractured legs were fixed in Zenker's fluid, which contained 10 per cent glacial acetic acid, and were further decalcified with 5 per cent nitric acid. Sections were taken from the aorta, heart, lungs, bronchi and costochondral junction of the ribs. These were likewise fixed in Zenker's fluid, blocked in paraffin and stained with phloxine<sup>9</sup> and methylene blue (methylthionine chloride U. S. P.). No special stains were made in studying the organs sectioned. The main object was to determine whether the varying doses produced any changes in the other tissues while attention was concentrated on the effect on bone and cartilage. Unlike most workers on this subject, I have been unable to demonstrate the marked calcareous lesions that have been reported. With the early small doses no changes were observed, but as the higher ranges were approached, renal and myocardial damage was evident. The renal changes observed will be reported on in a subsequent paper. Only a single instance of medial thickening of the aorta in the group given 15 mg. was seen, and one case of inflammatory infiltration was seen in the group given 10 mg.

*Fractured Bones and Costochondral Junction of the Ribs.*—The bones were studied in groups according to days of healing, so that approximately comparable changes could be observed within certain

8. Reed, C. I., and Thacker, E. A.: Effect of Intravenous and Intraperitoneal Injections of Irradiated Ergosterol. *Am. J. Physiol.* **96**:21 (Jan.) 1931.

9. Tetrabromodichlorofluorescein and tetrabromotetrachlorofluorescein.

periods postoperatively for different doses. I shall limit myself, at present, to an analysis of the data.

The striking observation histologically was the consistent stimulation of the osteogenic layer of the periosteum in the group of animals given a low dose. The sections in this study were divided into groups as shown in table 5. This does not include the animals of the groups given 5, 10 and 15 mg. that were killed in five days; these will be discussed separately. In this paper I am accepting the reaction of the osteogenic

TABLE 5.—*Correlation of Changes in Bones with Dosage of Viosterol*

Autopsy, Days Following Fracture	Control	1 Mg.	2 Mg.	5 Mg.*	10 Mg.	15 Mg.
14 to 16	Slight osteo- genic pro- liferation	Marked stimulation osteogenic layer; active mitoses; dif- ferentiation; hyaline cartilage	Repair more advanced than in group given 1 mg.; many osteoclasts and osteo- blasts	Periosteum stimulated; oste- myelitis present	Fibrous stimulation; osteogenic layer less stimulated; rib thickened	Fibrous stim- ulation as in osteitis fibrosa; slight thickening of ribs
25 to 28	Healing well advanced	Well advanced healing; endosteum thicker than in control	Almost complete healing; periosteum thicker than in animals given 1 mg.	Fibrous layer stimulated; slight osteogenic stimulation; osteitis fibrosa type	Less true bone for- mation; osteoid tissue present; fibrous stimulation advanced	Much fibrous proliferation; osteogenesis retarded; rib like that in osteitis fibrosa
36 to 40	Healing almost completed	Healing more advanced than in control	Healing complete	Healing advancing	Slight progress in healing; similar to that in ani- mals given 5 mg.	Fibroblastic proliferation; embryonic cartilage cells; appearance of rib as in oste- itis fibrosa
42 to 47	Completely healed	Completely healed	Completely healed	No marked evidence of osteitis fibrosa	Some osteitis fibrosa	

\* No changes in the costochondral junction of the ribs in groups given from 1 to 5 mg.

layer of the periosteum as the prime factor in bony regeneration. The experimental work appeared to bear out Ham's<sup>9a</sup> conclusions in his study of the early phases of bone repair. He drew a sharp line of difference between the outer fibroblastic layer of the periosteum and the inner osteogenic layer, which also lines the haversian canals and makes up the endosteum.

The control fracture at the end of fourteen days showed slight stimulation of the deeper layer of the periosteum, the so-called osteogenic layer, and proliferation of the outer fibroblastic cells which were growing into the site of fracture. The group given 1 mg. showed an increased

9a. Ham, A. W.: A Histological Study of the Early Phases of Bone Repair, *J. Bone & Joint Surg.* **12**:827 (Oct.) 1930.

stimulation of the osteogenic cells that was out of all proportion to that seen in the control animals. The maximum amount of stimulation and an advanced degree of bone repair were seen in the guinea-pig given 2 mg. Many mitotic figures were seen in the osteogenic layer, which became several cell layers in thickness. Differentiation into chondroblasts with extension of hyaline cartilage into the site of fracture was evident. Bone resorption and bone regeneration appeared to progress simultaneously. Numerous osteoclasts filled the bony trabeculae. The presence of osteomyelitis interfered with proper evaluation of the results

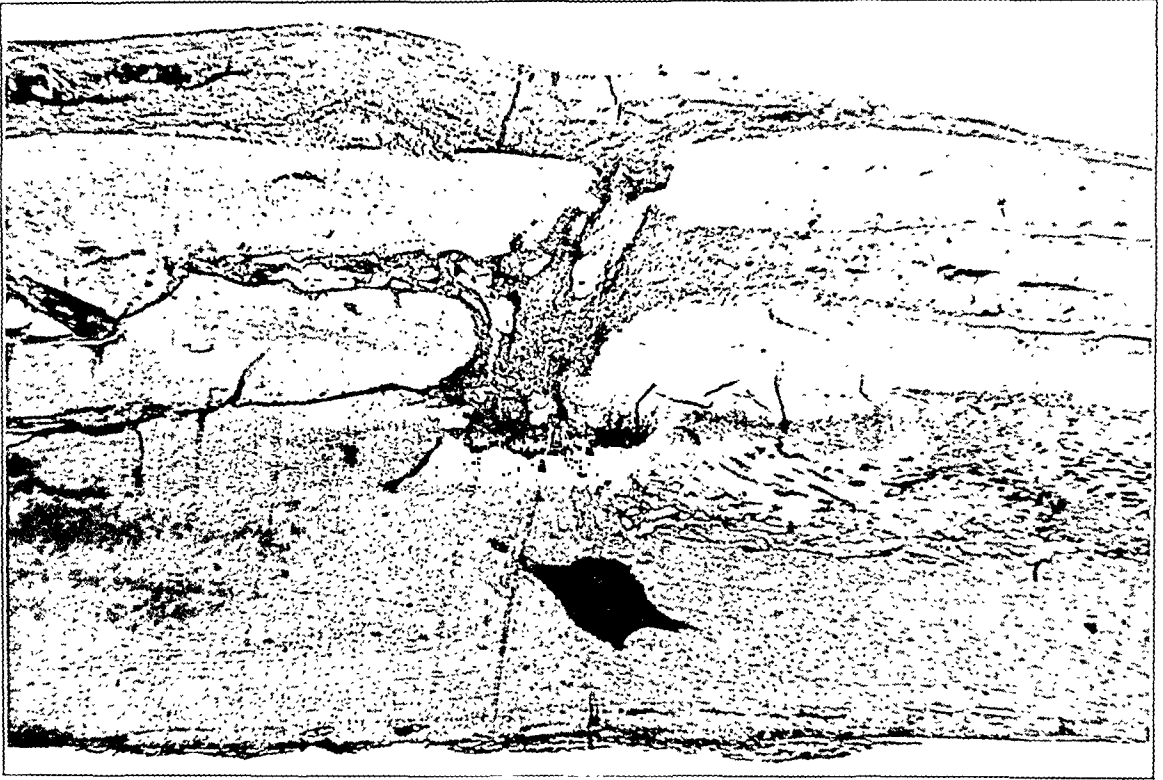


Fig. 1.—Control fracture after fourteen days, showing thickening of the periosteum and fibrous ingrowth into the site of fracture.

in the guinea-pig given 5 mg. I noted, however, even at this early date, that as the larger dose group was approached the degree of osteogenesis appeared retarded. In the animal given 10 mg., and to even a greater degree in the one given 15 mg., there appeared to be a complete reversal of the earlier observations. The outer or fibrous layer of the periosteum was stimulated largely, and the osteogenic layer was apparently retarded in its proliferative activities. There was no tendency whatever toward osseous formation in the animals given 15 mg. The fibrous areas contained numerous osteoclasts, but no osteoblastic activity was apparent. The picture presented here was one of early osteitis fibrosa.

In from twenty-five to twenty-eight days the changes outlined in the fourteen to sixteen day group were apparent in a more advanced degree. The maximum amount of healing appeared in the group given 2 mg., while fibrous stimulation was more marked in the groups given the higher doses, so that osteogenesis completely retarded by fibrous ingrowth was found, with no differentiation of the early fibroblasts into osteoblasts. The lacunar spaces were filled with fibrous tissue.

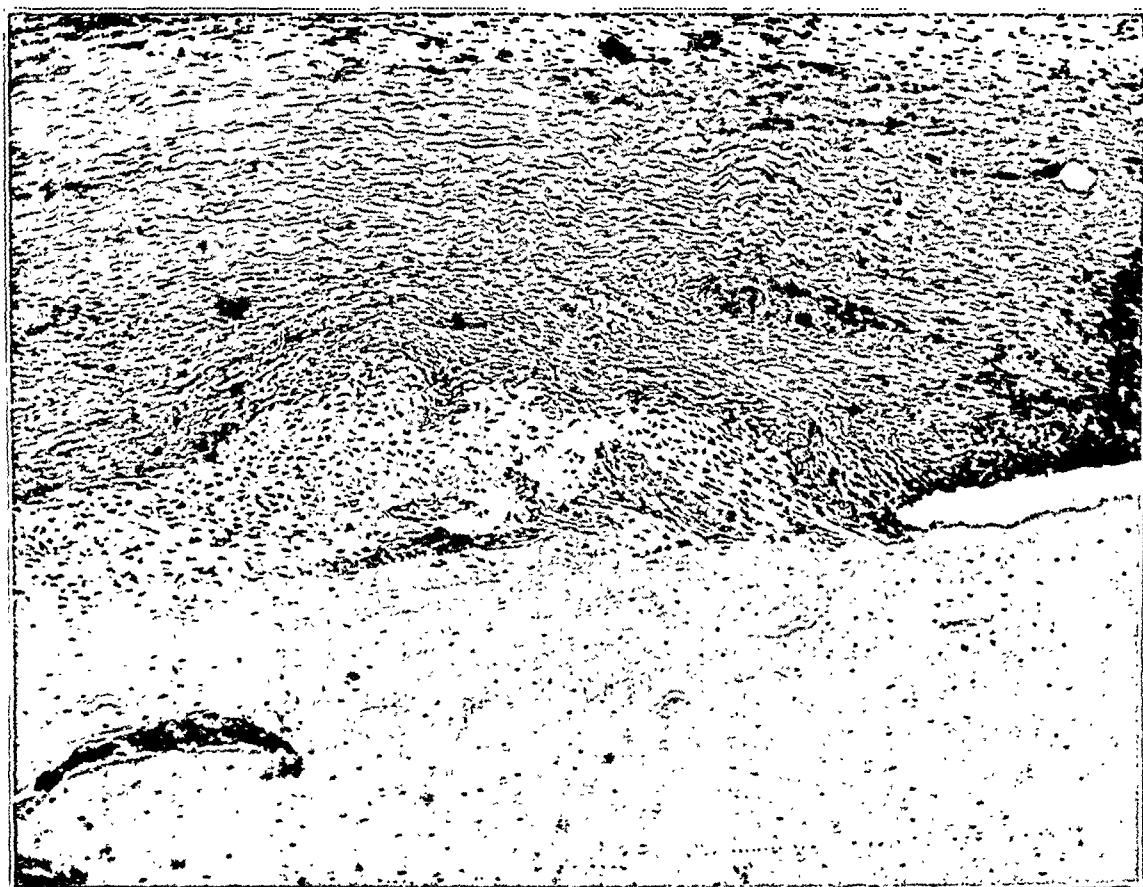


Fig. 2.—Higher power magnification of the control fracture after fourteen days, showing only slight stimulation of the osteogenic layer.

As the thirty-six to forty and forty-two to forty-seven day animals were studied, a change was noted only in the group given 5 mg. Here the fibrous stimulation was retarded, and bony healing advanced to completion. But the animals given 10 and 15 mg. presented fibrous proliferation and the true picture of *osteitis fibrosa*.

The ribs failed to show any changes at the costochondral junctions when the small doses were given, but as the higher doses (from 10 to 15 mg.) were approached the changes were marked. They resembled

in all particulars a true picture of osteitis fibrosa with the exception that no cysts or osteoid tissue was present.

As Jaffe and his co-workers<sup>10</sup> pointed out, the presence of cysts is not essential for a diagnosis of osteitis fibrosa, their presence representing merely an older lesion in which repair is attempted. Otherwise the condition produced was identical with that seen in the human being. The costochondral areas were greatly thickened, owing to considerable fibroblastic proliferation. The fibroblasts extended into the surrounding



Fig. 3.—Fracture after fourteen days in animal that received 2 mg. of viosterol daily. Marked periosteal thickening is present.

muscle fiber interstices as well as into the marrow spaces which contained areas of hemorrhage. There was marked perichondral thickening.

The sections of bone and rib in the five and nine day groups were obtained only from the animals given higher doses. As no comparable sections were present in the group given lower doses, no study was made.

10. Jaffe, H. L.; Bodansky, A., and Blair, J. E.: Fibrous Osteodystrophy (Osteitis Fibrosa) in Experimental Hyperparathyroidism of Guinea-Pigs, *Arch. Path.* **11**:207 (Feb.) 1931.

## COMMENT

Considerable controversy has arisen since the introduction of viosterol as to its effect on the calcium and phosphorus content of the blood serum. Its relationship to bone repair has also been stressed numerous times. In considering the varying results obtained by numerous workers, one must bear in mind the different factors that determine variation in the serum calcium.

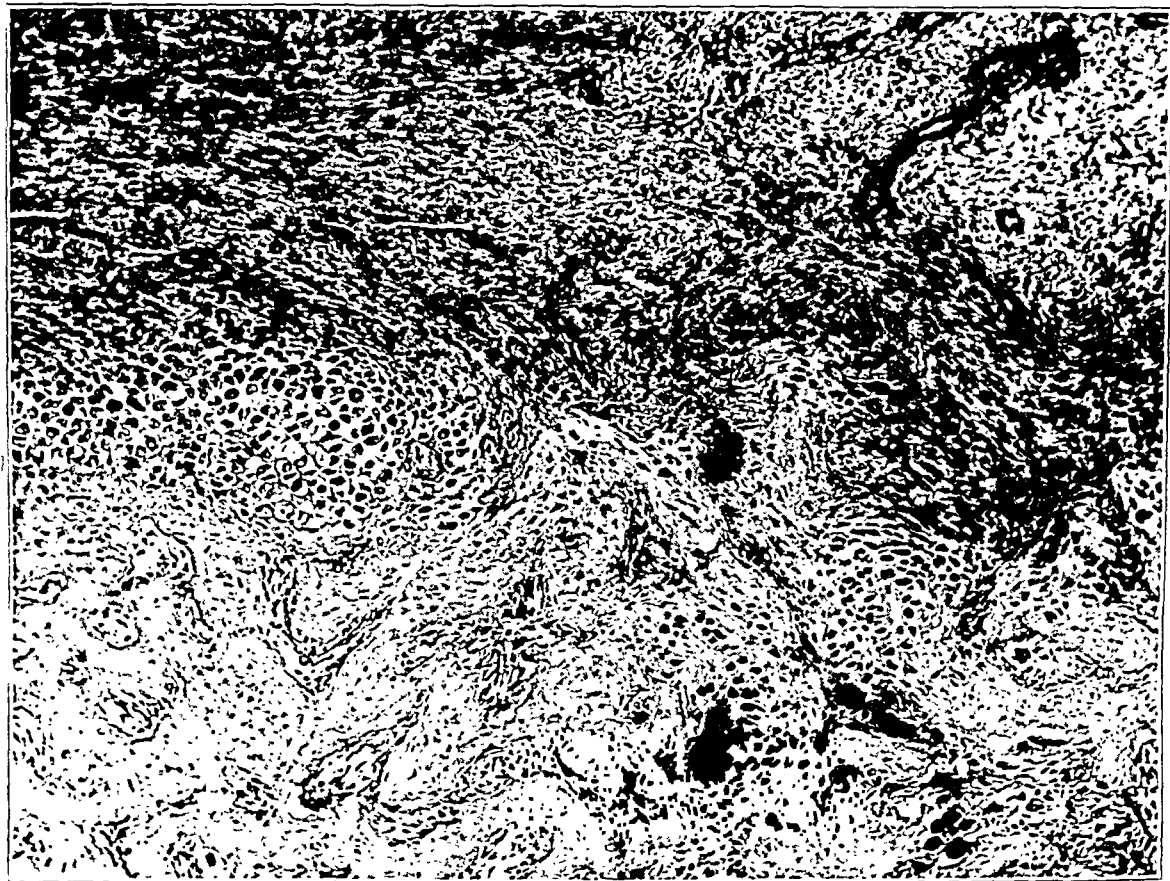


Fig. 4.—Stimulation of the osteogenic layer of the periosteum to several cell layers in thickness in guinea-pig that received 2 mg. viosterol daily.

Duguid and his co-workers<sup>11</sup> found viosterol to be more toxic for rats fed on a synthetic vitamin-free diet of high calcium content than for those fed on a normal diet of bread and potatoes. Likewise, normal animals<sup>12</sup> as well as human beings<sup>13</sup> appear to be more susceptible to

11. Duguid, J. B.; Dugan, M. M., and Gough, J.: Toxicity of Irradiated Ergosterol, *J. Path. & Bact.* **33**:353 (April) 1930.

12. Brown, H. B., and Shohl, A. T.: Alteration of Calcium and Phosphorus Metabolism of Normal and Ricketic Rats, *J. Biol. Chem.* **86**:245 (March) 1930.

13. Thatcher, L.: Hypervitaminosis D: Fatal Case in Child, *Edinburgh M. J.* **38**:457 (Aug.) 1931.

the untoward effects of viosterol than do rachitic subjects. Various animals react differently to graded doses. Thus the toxic dose for the rat or rabbit is nontoxic for the guinea-pig.

I have attempted to explain the variations in the initial rise and ultimate fall in the serum content of calcium and phosphorus in overtreated animals on the basis of absorption from the intestine and excretion in the urine. Vitamin D in small or moderate doses appears to increase

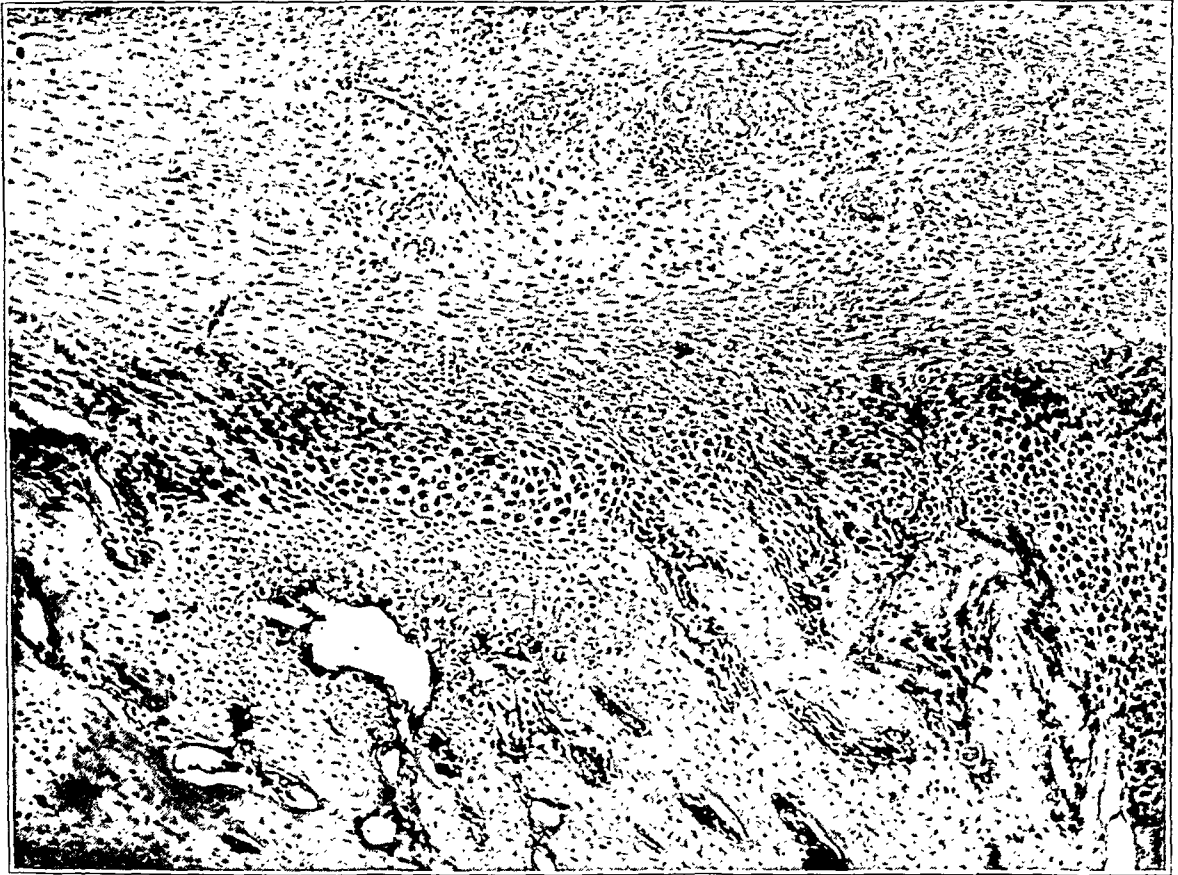


Fig. 5.—High power magnification, showing stimulation of the osteogenic cell layer and chondroblastic differentiation in an animal that received 1 mg. of viosterol for fourteen days.

the amount of absorption of calcium from the intestinal tract. This apparently continues until a certain level is reached, when calcium begins to be increased in the urine. Haines and Innes<sup>14</sup> suggested that the increased excretion occurs when the phosphorus rises above a certain threshold. They believed that the excretion in the urine was, as time

14. Haines, L. J., and Innes, J. R. M.: The Mode of Action of Vitamin D. Studies on Hypervitaminosis D. The Influence of the Calcium Phosphorus Intake, *Biochem. J.* **25**:367, 1931.



went on, greater than the absorption from the intestines. This mechanism does not appear to explain all the facts.

I observed that as the amount of viosterol administered to the subject was increased, the increase in the blood serum values was not proportional to the increased dosage. With the higher doses the bones showed marked evidence of decalcification and resorption. The question here arises as to whether there is a difference in the mode of action of small doses of viosterol and of toxic doses as to the manner of absorp-

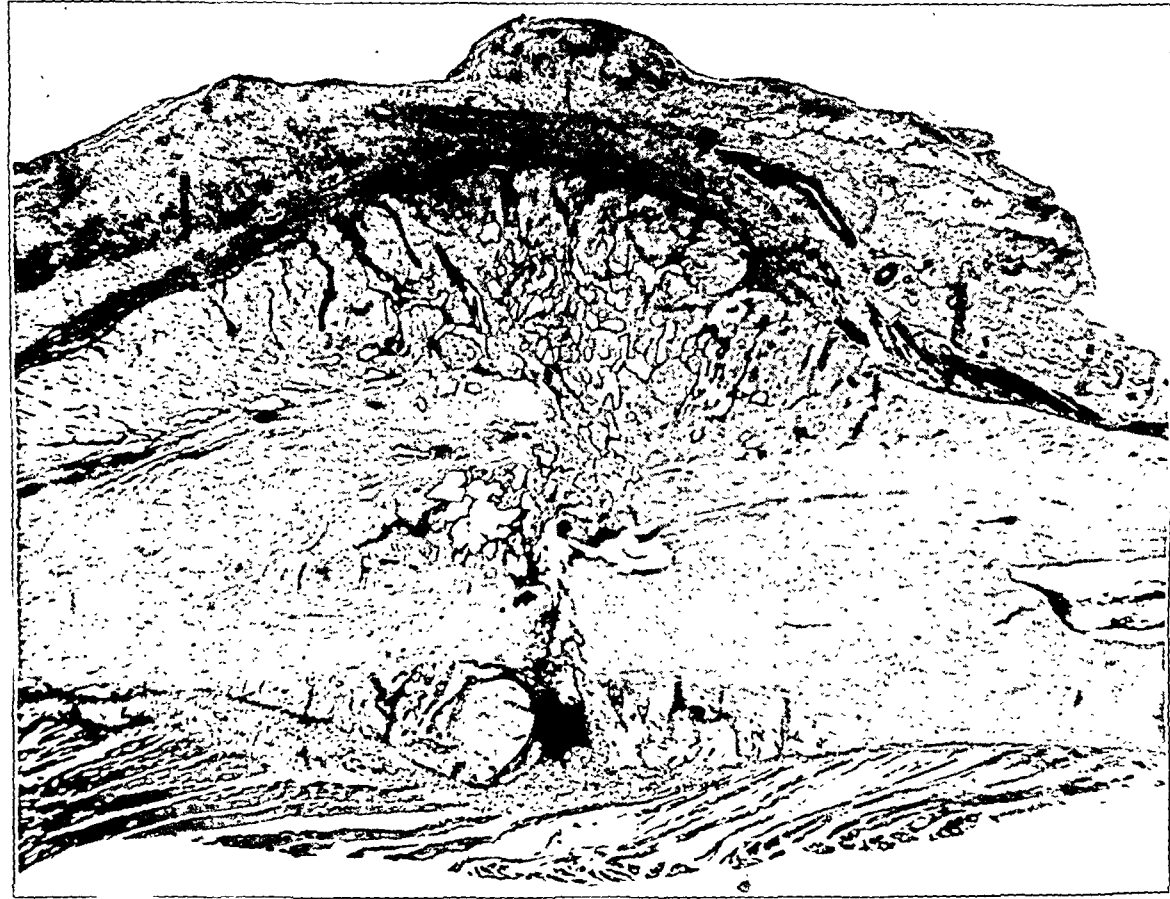


Fig. 6.—Fracture completely healed after twenty-eight days. The guinea-pig received daily doses of 2 mg. of viosterol.

tion and excretion of the calcium with relation to the intestines, body tissues, blood serum and urine. Several observations in the present work and those gleaned from other workers appear to emphasize a marked difference at various levels of dosage. Hess, Weinstock and Rivkin<sup>15</sup> produced depletion in the serum calcium in young rats fed on a diet

15. Hess, A. F.; Weinstock, M., and Rivkin, H.: Source of Increase in Serum Calcium Induced by Irradiated Ergosterol, *Proc. Soc. Exper. Biol. & Med.* **26**: 199 (Dec.) 1928.

containing a calcium-phosphorus ratio of 1:500. Thereafter the feeding of large amounts of viosterol brought about an increase of 50 per cent in the serum calcium. Apparently, then, the calcium came from the body tissues, as these animals received only 0.8 mg. of calcium and 400 mg. of phosphorus daily. Watchorn<sup>16</sup> fed excessive doses of viosterol to rats and studied the absorption and excretion of the calcium and phosphorus in the urine and feces. She observed that the urinary calcium was increased in amount while the fecal calcium was decreased.

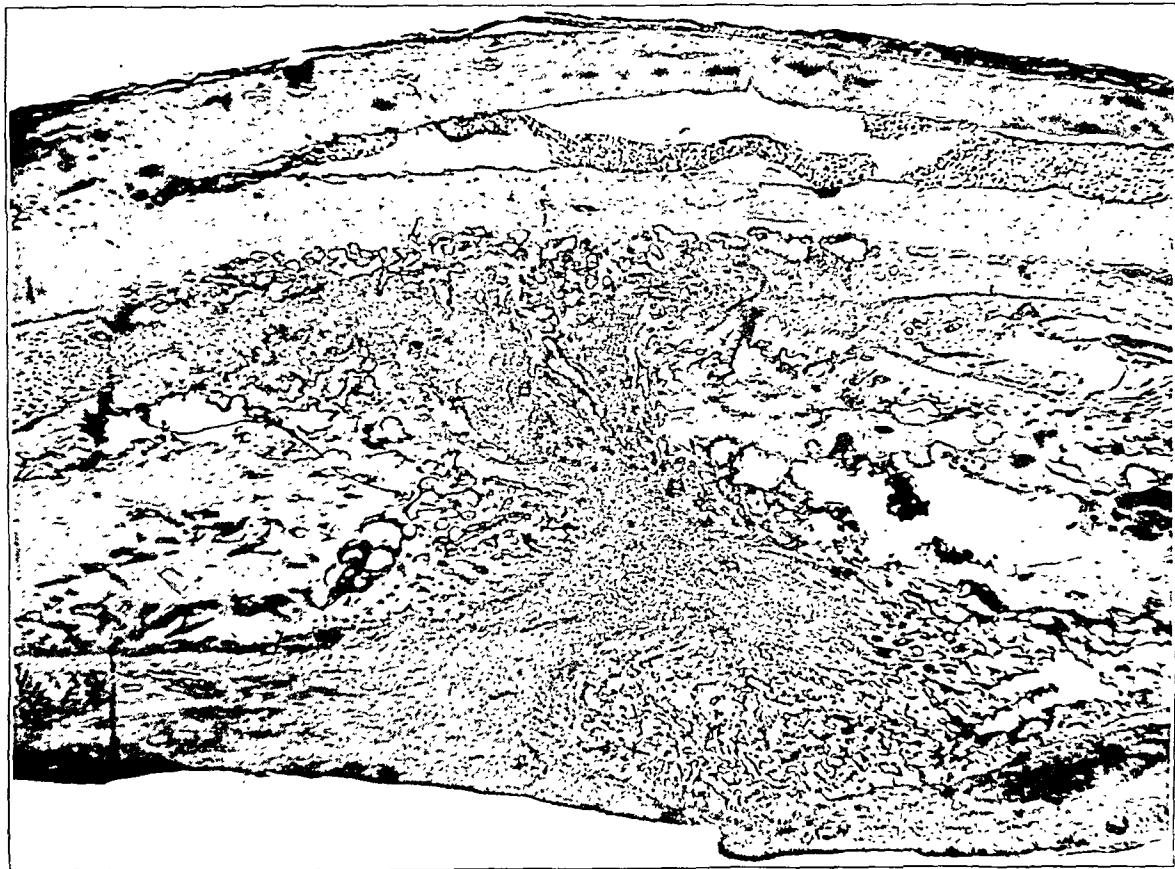


Fig. 7.—Fibrous union with the presence of osteoid tissue in animal that received daily toxic doses of 10 mg. of viosterol for twenty-five days. No bony union is noted.

Not much change was observed in the phosphorus values. In the after-periods, however, the urinary calcium decreased while the fecal calcium increased.

In the light of these observations, I have concluded that in small therapeutic and in moderate doses vitamin D causes absorption of calcium from the intestinal tract and thus reduces the amount of fecal

16. Watchorn, E.: The Absorption and Excretion of Calcium and Phosphorus by Rats Receiving Excessive Doses of Irradiated Ergosterol, *Biochem. J.* **24**:631, 1930.

calcium and increases the urinary calcium. This continues either until the amount of serum calcium reaches a certain level or until larger, so-called toxic, doses are employed. At this point the amount of calcium available from the intestinal tract is exhausted, and the body tissues and bones are called on to supply calcium commensurate with the increased dosage of viosterol; whereupon the fecal calcium content again returns to within its former limits and the body tissues, particularly the bones, begin to show evidences of decalcification. This

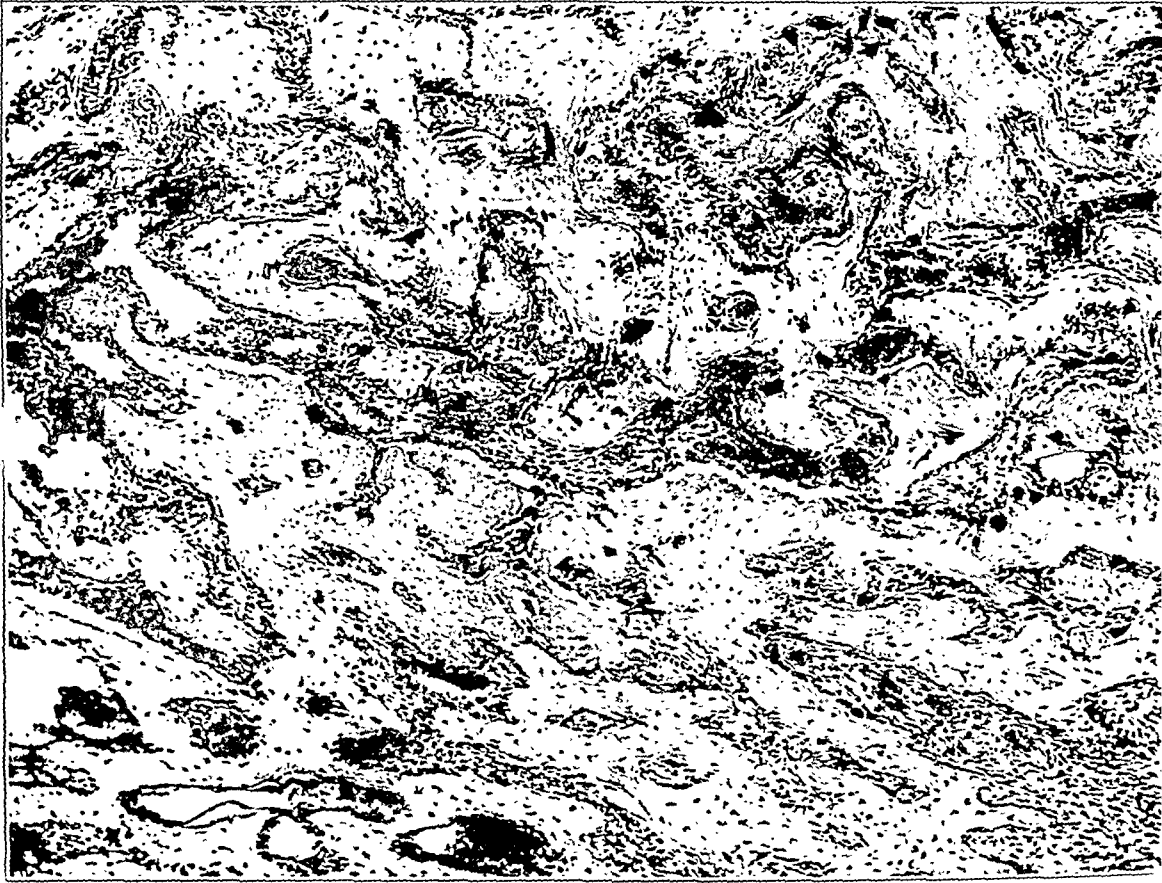


Fig. 8.—Higher power magnification of figure 7, showing beginning osteitis fibrosa. The lacunar spaces are filled with fibrous tissue and hemorrhagic areas are seen.

explains the evidences of marked bone decalcification and maintained serum calcium levels in the present study. I have also observed differences in the action of small and large doses of viosterol in bone repair.

The theory of Petersen<sup>17</sup> was not borne out in the present work. I found an increased calcium-phosphorus product in the high dosage group

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17. Petersen, H. A.: Experimental Study of Ununited Fractures with Especial Reference to Inorganic Bone-Forming Elements in Blood Serum, *Bull. Johns Hopkins Hosp.* 35:378 (Nov.) 1924.

when bone repair was definitely retarded, contrary to Petersen's former ideas. In place of a diminished calcium-phosphorus product of 30 or less, I found that the products varied from 55 to 60. In fact, the higher the product, the result of increased calcemia and phosphotemia, the more retarded was the bony regeneration. The serum values cannot be regarded as individual factors isolated from other considerations, since the question of calcium metabolism is extremely complex and involves many of the bodily activities that do not appear to be concerned with



Fig. 9.—Costochondral junction of a normal control rib.

the repair of bone. Speed<sup>18</sup> failed to confirm Petersen's conclusions while altering the calcium and phosphorus values in dogs in which experimental fractures were produced. Likewise the work of Ravdin and Jonas<sup>19</sup> in human beings has shown the futility of attempting to prognosticate union or failure of union after fracture by computing the calcium-phosphorus product.

18. Speed, K.: In Relation to Blood Serum Calcium, *J. Bone & Joint Surg.* **13**:58 (Jan.) 1931.

19. Ravdin, I., and Jonas, L.: Studies of Calcium and Phosphorus Metabolism in the Fracture of Bones, *Ann. Surg.* **1**:84, 1926.

The studies of the fractured bones in the animals that received viosterol as compared with the normal controls caused me to believe that osteogenesis was stimulated by vitamin D through differentiation of the osteogenic cells. In the group of animals given low doses the first step in the repair of the fracture was marked proliferation of the osteogenic cells, followed by differentiation into chondroblasts and osteo-

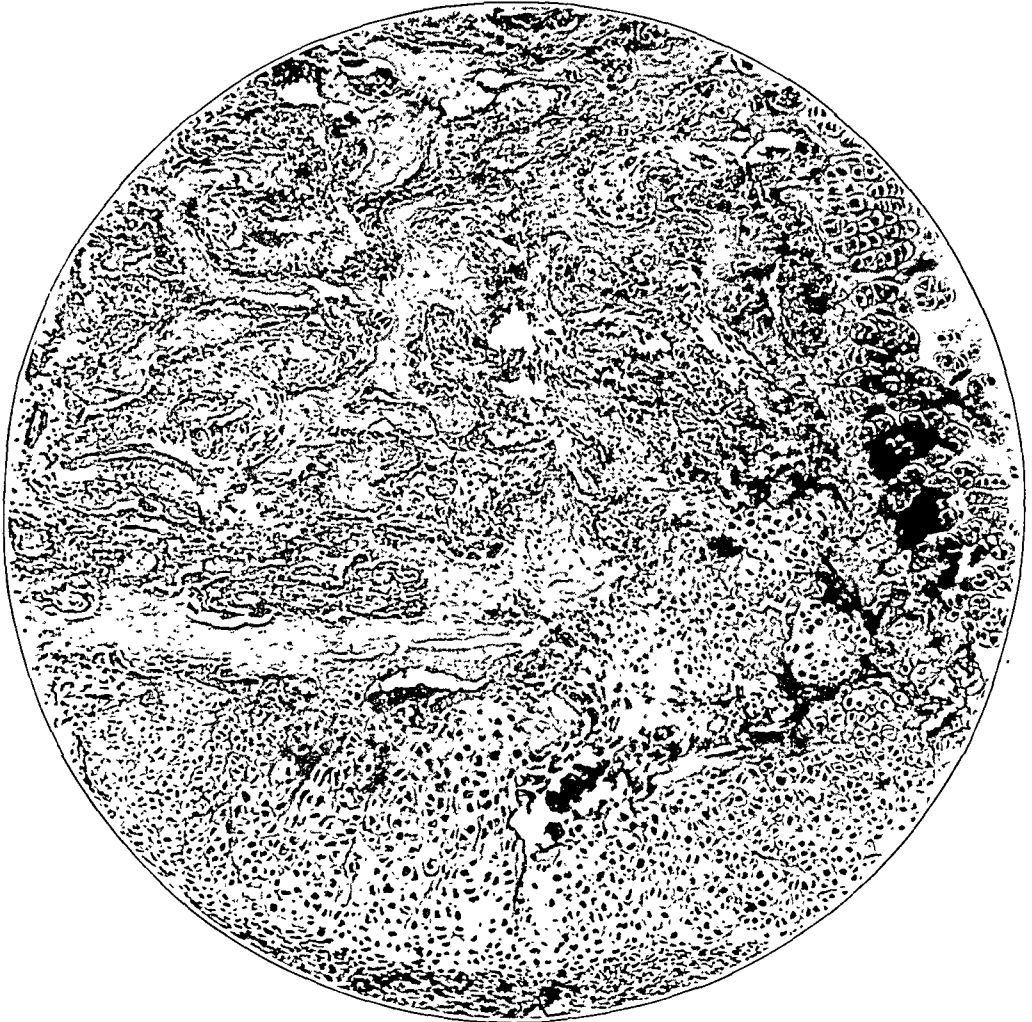


Fig. 10.—Costochondral junction of a rib from a guinea-pig that received 15 mg. of viosterol daily for twenty-five days. The bone marrow is completely replaced by dense fibrous connective tissue, and cartilaginous overgrowth is apparent.

blasts. On the other hand, in the group given high doses the fibrous layer was stimulated to proliferation while the osteogenic layer was retarded in both its proliferative and its differentiating activities.

To explain these differences, I have formulated a theory in regard to the enhancement of differentiation through calcium-producing factors.

When the periosteum was torn following a fracture, the cells in both the osteogenic and the fibrous layer initiated proliferative activity to bring about repair. With the introduction of vitamin D through the agency of viosterol, stimulation was produced which was necessary to bring about more marked osteogenic cell proliferation and ultimate differentiation. The reason for selective stimulation of the osteogenic cells to a greater degree than the more mature outer fibroblastic cells is based on the fact that the former, being more embryonic in type, still maintain the proliferative properties of early cells. Differentiation can occur only under optimum conditions, among which a good blood supply is



Fig. 11.—Evidence of decalcification with bone resorption and cyst formation is seen in the corticalis. Toxic doses of 15 mg. were administered daily for twenty-five days.

of paramount importance. Furthermore, with the introduction of a calcium-producing factor, differentiation into the chondroblasts and ultimate osteoblasts naturally follows, as has been observed in bone formation in the fetus. H. A. Harris<sup>20</sup> considered that "this process of cell differentiation for function is in part attributable to arrival in the area, via the blood stream, of fat soluble, blood borne substances." He regarded this substance as fat-soluble vitamin A. The same author

20. Harris, H. A.: Bone Formation and the Osteoblast, *Lancet* 2:489, 1928.

considered that vitamin D is concerned only with calcification and not with differentiation.<sup>21</sup> Haines and Innes, on the other hand, found that there was marked stimulation of new bone formation in long bones with moderate overdosage of viosterol (vitamin D) before toxic symptoms appeared. My histologic studies of osteogenesis bear out this observation. In confirmation of my observations Bacharach<sup>22</sup> found that the addition of vitamin D to a diet free from fat-soluble vitamins definitely improved the rate of growth, while the addition of vitamin A stimulated

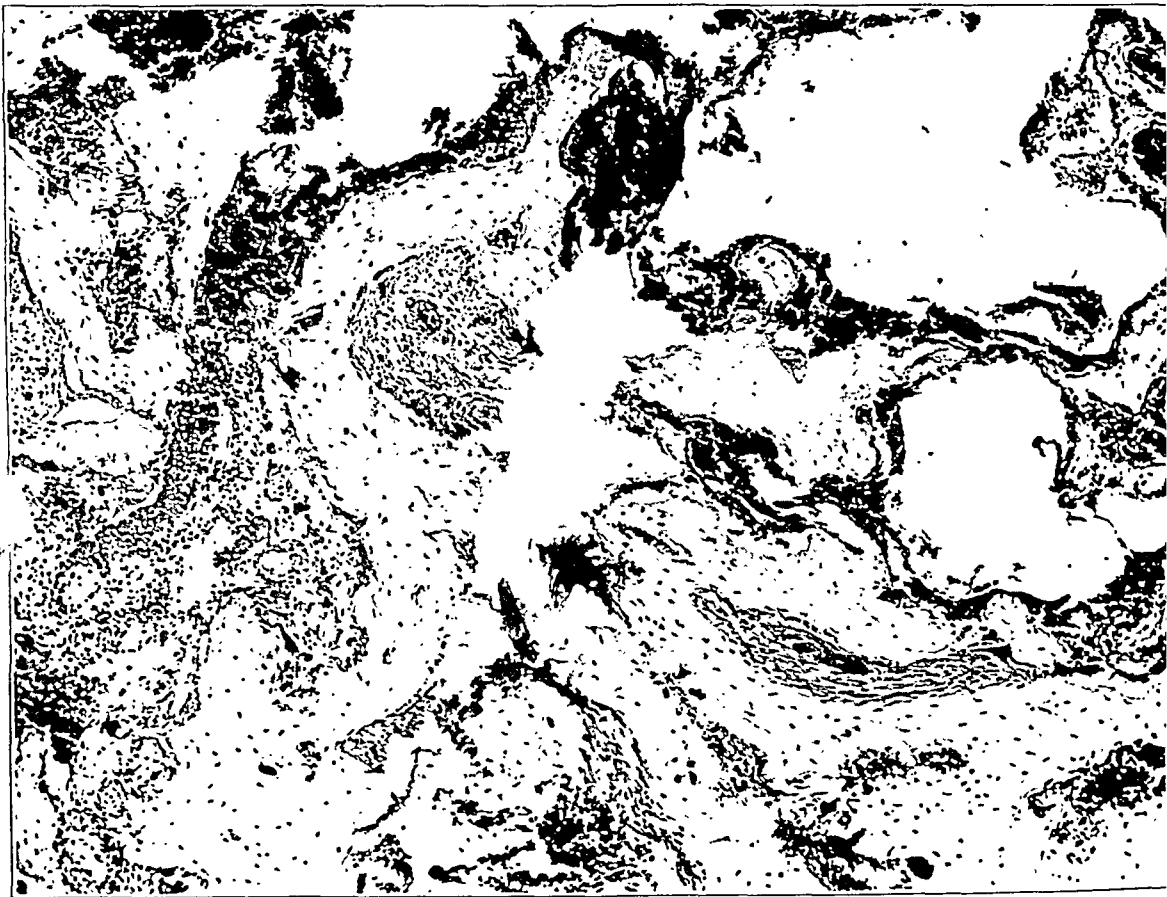


Fig. 12.—High power photomicrograph, showing resorption of bone, fibrous ingrowth into the lacunar spaces, hemorrhages and cyst formation in the bone of a guinea-pig that received 15 mg. of viosterol daily for thirty-six days.

growth only slightly. A combination of vitamins A and D stimulated growth as in the normal subject on a basal diet.

When doses of from 10 mg. to 15 mg. were employed, the costochondral junction of the ribs and the long bones showed changes that

21. Harris, H. A.: Cod Liver Oil and Vitamins in Relation to Growth, *Am. J. M. Sc.* **181**:453 (April) 1931.

22. Bacharach, A. L.: The Growth Promoting Properties of Vitamin D, *Quart. J. Pharm. & Pharmacol.* **1**:49, 1928.

were similar to those seen in osteitis fibrosa. The pictures produced were much like those described by Jaffe, Bodansky and Blair. In their earlier work Jaffe and Bodansky<sup>23</sup> employed young puppies that were kept on a low calcium diet so that parathyroid extract-Collip could be administered over a long period of time. In the dog, doses of parathyroid extract necessary to produce marked resorption of bone are apt to lead to a fatal hypercalcemia before there is much fibrous repair. Although guinea-pigs are not truly immune to the action of parathyroid extract, and in my cases to viosterol, they exhibit an ability to excrete calcium sufficiently rapidly so that fibrous repair of bone can be initiated. This explains the marked stimulation of the fibrous layer in the group of animals given high doses. As the toxic doses were approached, decalcification of bone resulted. With decalcification fibrous replacement was brought about by way of proliferation and ingrowth of the fibroblasts comprising the outer periosteum.

Vitamin D, as employed by means of viosterol, appears to be the counterpart of the hormone of the parathyroid gland. In animals in which vitamin D was employed I have observed numerous changes that have been described by workers employing parathyroid extract. A comparative study of these two related substances is not within the scope of this paper.

In closing I may note that some therapeutic application of the use of viosterol may be present in early fractures, not as a means in itself, but as an adjunct to treatment. First, an adequate blood supply is essential. Knoflach<sup>24</sup> administered viosterol to fifty-one patients with various fractures and studied thirty-one as controls. From 5 to 10 mg. was given twice daily, depending on the age of the patient, and weekly roentgenograms were taken. No roentgen changes were present in the group of children that were studied, but a slight shortening of the time required for the uniting of the fractures was observed. The group from 18 to 55 years of age showed more callus in roentgenograms but no shortening in the time required for healing. The group over 55 years of age showed the greatest response. Here the time for healing was shortened below that for the younger group.

#### CONCLUSIONS

1. Viosterol, in therapeutic doses, causes stimulation of the osteogenic layer of the periosteum in experimental fractures.
2. Osteogenic differentiation is enhanced through the agency of viosterol (vitamin D).

23. Jaffe, H. E., and Bodansky, A.: *Experimental Osteitis Fibrosa Cystica in Dogs*, *Proc. Soc. Exper. Biol. & Med.* **27**:795, 1930.

24. Knoflach, S. G.: *Behandlung der Knochenbrüche mit bestrahltem Ergosterin*, *Wien. klin. Wchnschr.* **41**:739 (May 24) 1928.



3. Overdosage produces stimulation of the fibrous layer of the periosteum through decalcification of bone, and causes retardation in repair.

4. Osteitis fibrosa is simulated by overdoses of viosterol in guinea-pigs.

5. Studies of the serum calcium and phosphorus in the case of high doses invalidate the calcium-phosphorus product as a means to prognosticate nonunion.

6. A theory as to the mode of action of viosterol in experimental fractures is advanced whereby the osteogenic layer is stimulated to differentiation and proliferation by small doses of viosterol following the initial impetus toward repair produced by the fracture.

Dr. Samuel R. Haythorn, Director of the William H. Singer Memorial Research Laboratory, prepared the accompanying photomicrographs, and Dr. Charles N. Frey, of the Fleischmann Laboratory, assisted in preparing the irradiated ergosterol used in the experimental work.

# DUODENAL TUBERCULOSIS

A REVIEW OF THE LITERATURE AND REPORT OF A CASE OF  
HYPERPLASTIC TUBERCULOSIS OF THE DUODENUM

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Duodenal tuberculosis, even as a part of advanced generalized tuberculosis, is an unusual finding. Tuberculous disease of the duodenum, as an entity in itself and causing symptoms per se, is a very rare occurrence. The duodenum seems to be spared even when most of the remaining gastro-intestinal tract is involved. Perry and Shaw (1894), studying a series of 17,652 cases in which autopsy was done in Guy's Hospital in a period of sixty-six years, found only 11 cases of duodenal tuberculosis. Fenwick and Dodwell (1892) performed autopsy in 2,000 cases of pulmonary tuberculosis, 500 of which showed intestinal ulceration but in only 3.4 per cent (or 17) of this 500 was there duodenal involvement. Schwatt and Steinbach (1923), in 199 cases of pulmonary and generalized intestinal tuberculosis found 3 in which the duodenum was involved. Gossmann (1913) performed autopsy in 2,360 cases of tuberculosis, only 5 of which showed duodenal lesions. In all of these reports, and, in fact in most of the cases of tuberculosis described, the duodenal lesions when found were merely incidental in the whole picture of advanced terminal tuberculosis. We were able to find 105 such cases in a careful survey of the literature. In addition to the authors just named, writers reporting cases of this kind are: Leudet (1853), Rintel and Schultzen (1867), Clark (1867), Hebb (1891), Claude (1896), Kirkorow (1899), Satterthwaite (1900), West (1909), Kraus, Moynihan (10 cases) (1910), Sachaczewski (1909), Pagel (3 cases) (1924-1925), Buckley (1927), Reeves (1931), Francine (2 cases) (1905), Weiting (1905), Engelsmann (9 cases) (1918), Ricard and Chevrier (10 cases) (1905), Fowler and Godlee (7 cases) (1898). Powell and Hartley (6 cases) (1921), Krug (7 cases) (1900).

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This work has been conducted under a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago.

On the other hand, we found only 18 cases of duodenal tuberculosis producing local symptoms. These are listed in the accompanying table. It is noteworthy that in only 6 of these cases was the tuberculous nature of the lesion verified histologically. Of these 18, 6 were associated with generalized active tuberculosis, and 12 were either primary or the only apparent active lesions in the body. These 18 cases, added to the 105 previously mentioned, make a total of 123 cases of duodenal tuberculosis in the literature. All of these, save one, are instances of either ulcerative or caseous disease. The only report of hyperplastic tuberculosis of the duodenum is that of Garvin in 1930. He was not able to confirm his diagnosis by microscopic examination, but the clinical and operative findings were so typical of this disease that little doubt can be held that his diagnosis was correct. The case presented here is therefore the second to be reported.

#### REPORT OF A CASE

*History.*—W. O., 57 years old, a nightwatchman, of Norwegian descent, presented himself for treatment in September, 1930. The family history was unimportant except that a sister died at 19 of tuberculosis. The patient's personal habits were good. His marital history was unimportant. He told of an indefinite thoracic disease five to six years before, supposedly pleurisy. The anamnesis was otherwise irrelevant until the onset of the present illness. This was attributed to a severe "cold" about seven to eight months before he entered the hospital. Following this, he complained of loss of appetite, progressive loss of weight and strength and increasing discomfort in the epigastrium. Small amounts of food produced a sensation of fulness which was followed by repeated vomiting. The discomfort was not relieved by alkalis.

*Examination.*—The significant physical and laboratory findings were as follows: There was slight tenderness in the epigastrium but no palpable tumor. The Wassermann and Kahn tests were negative. The urine was normal. The blood examination revealed: erythrocytes, 4,120,000; leukocytes, 9,000, and hemoglobin, 82 per cent. Occult blood was repeatedly found in the stools. Gastric analysis after an Ewald test meal revealed no free hydrochloric acid and a total hydrochloric acid of 11 clinical units. An alcohol test meal also yielded no free acid, and none appeared after stimulation by histamine. Gastric fluoroscopy showed a filling defect in the pyloric antrum without obstruction. Roentgenograms of the chest revealed several calcified areas in the middle third of the right lung but no signs of active pulmonary tuberculosis.

*Operation.*—A diagnosis of probable carcinoma of the stomach was made, and the patient was operated on Sept. 23, 1930, by one of us (Dr. Dragstedt). A smooth, firm mass about 4 by 3 cm. was found in the anterior wall of the first portion of the duodenum and extending to the pyloric sphincter (fig. 1). The neighboring lymph glands were not enlarged, and no other lesion was found in the abdomen. In consistency, the tumor resembled the normal pancreas, and the possibility that it might be an aberrant or duodenal pancreas was kept in mind. Because of the symptoms of pyloric obstruction, the persistence of blood in the stools and the absence of free acid in the gastric contents, it was thought wise to resect the first portion of the duodenum and the pyloric portion of the stomach. The intestinal continuity was reestablished by a modified type of polya anastomosis.

# Cases of Duodenal Tuberculosis Causing Local Symptoms

Author	Sex	Age	Symptoms	Tuberculosis Else-where in Body	Pathologic Findings
1. Trier..... (1863)	M	51	Hematemesis; pain like peptic ulcer for years	Arrested pulmonary	Perforating ulcer of first part of duodenum
2. Murchison.... (1869)	M	49	Repeated hematemesis	Active pulmonary	Ulcer of first part of duodenum, perforating into the pancreas
3. Perry and Shaw (1894)	M	56	Epigastric distress after eating, 3 weeks before death	Active pulmonary and miliary	Perforating ulcer of first part of duodenum
4. Margarrucci.. (1899)	M	65	Pyloric obstruction	Stricture of ileum	Scar tissue stricture of first part of duodenum
5. Satterthwaite (1900)	M	36	Pain and vomiting after eating for 5 years	Active pulmonary and intestinal	Not described
6. Hoche..... (1903)	M	?	Malena several days ante mortem	Active pulmonary	"Hemorrhagic ulcerations duodenum"; gross and microscopic confirmation of diagnosis
7. Blad..... (1910)	M	41	Hematemesis; distress after eating for 11 years	None ?	Ulcer of first part of duodenum; tubercles in the duodenal serosa; histologic confirmation of diagnosis
8. Moynihan.... (1910)	M	49	Symptoms of peptic ulcer for many years	None ?	Ulcer of first part of the duodenum penetrating the liver; serosal tubercles near the ulcer; histologic confirmation of diagnosis
9. Henle..... and (1912) 10.	Not given		Symptoms of duodenal stenosis (below ampulla of Vater ?)	Not mentioned	Strictures of the duodenum
11. Raymond et al. (1921)	M	44	Distress 2 to 3 hours after eating for 6 years	Arrested pulmonary	Abscess of retroperitoneal lymph gland, involving the walls of the adjacent first part of the duodenum; histologic confirmation of the diagnosis
12. Hart..... (1919)	F	?	Symptoms of pyloric obstruction	Not mentioned	Ulcer and stricture of first part of the duodenum
13. Loew..... (1922)	F	39	Marked evidence of pyloric obstruction 5 months	Arrested pulmonary and mesenteric	"Stricturing ulcer of the duodenum"; histologically tuberculous
14. Röpke..... (1928)	F	25	Symptoms of common peptic ulcer	None found	Ulcer and stenosis of first part of the duodenum; grossly and histologically tuberculous
15. Cohen..... (1928)	M	15	Spasmodic attacks epigastric pain for years	Caseous involvement of mesenteric glands	Fist-sized mass of duodenum; tubercles in neighboring lymph gland
16. Fischer..... (1929)	F	10	Symptoms of pyloric obstruction for 8 months	Cervical lymphadenitis; tuberculous osteomyelitis of humerus	Dense scar stenosis of first part of duodenum
17. Fischer..... (1929)	F	9	Symptoms of pyloric obstruction 3 months	Active pulmonary	Constricting scar first part of duodenum; typical (grossly) tubercles in serosa over the scar
18. Garvin..... (1930)	M	26	Symptoms of pyloric obstruction	Hyperplasia of ileum	Indurated stricture first part of duodenum; tubercles (by gross examination) in serosa overlying the lesion

An abscess developed near the hilus of the right lung shortly after the operation. The patient steadily became weaker and finally died on November 12.

*Autopsy.*—Autopsy was performed by Dr. Paul R. Cannon. The more important anatomic observations were as follows: unresolved pneumonia of the lower right lobe with central abscess, anastomosis between the stomach and jejunum well healed and the lumen patent, encapsulated calcified tuberculous nodules in the hilus of the right lung, arrested calcified caseous tuberculosis of the entire left kidney with complete obliteration of the left ureter by fibrocalcereous tuberculosis, healed tuberculosis of the seminal vesicles and the left tunica vaginalis testis. No lesions

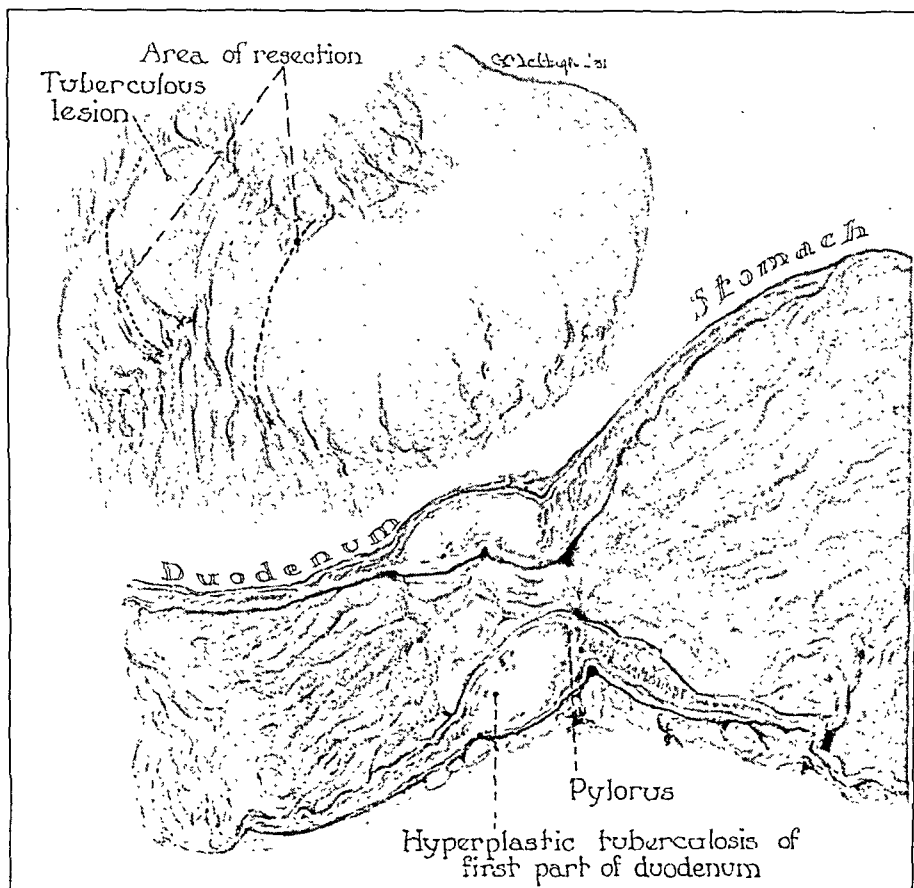


Fig. 1.—Drawing showing the gross appearance of the lesion in situ (upper portion) and (lower portion) a longitudinal section through the pylorus and first part of the duodenum.

similar to the one excised from the upper portion of the duodenum were found in the remainder of the gastro-intestinal tract.

The specimen removed at operation consisted of the first 2.5 cm. of the duodenum and terminal 4.5 cm. of the stomach. The serosa was smooth and glistening, not abnormally discolored, and apparently not involved in the disease process inside. By palpation of the stomach portion of the specimen, one found little abnormal beyond a moderate thickening and toughening of the wall near the pyloric ring. The duodenal segment, however, was much thicker and firmer than normal, the increase in thickness encroaching on the lumen so that the tip of the little finger

could be inserted only with difficulty. The greatest circumference of the duodenum here was (in the fixed specimen) 7 cm.

Surfaces made by cutting through the duodenum were whitish-pink and firm. The increased thickness of the wall completely encircled the lumen, being 1.2 cm. posteriorly and slightly less anteriorly. The tissue composing the thickening was perfectly homogeneous. Grossly, it extended from the serosa to the lumen and longitudinally from the pyloric ring to from 2 to 2.5 cm. beyond, where it decreased in thickness and the intestine assumed its normal size. Proximal to the pylorus the stomach was about 1 cm. thick, not so firm as the duodenum, and the different

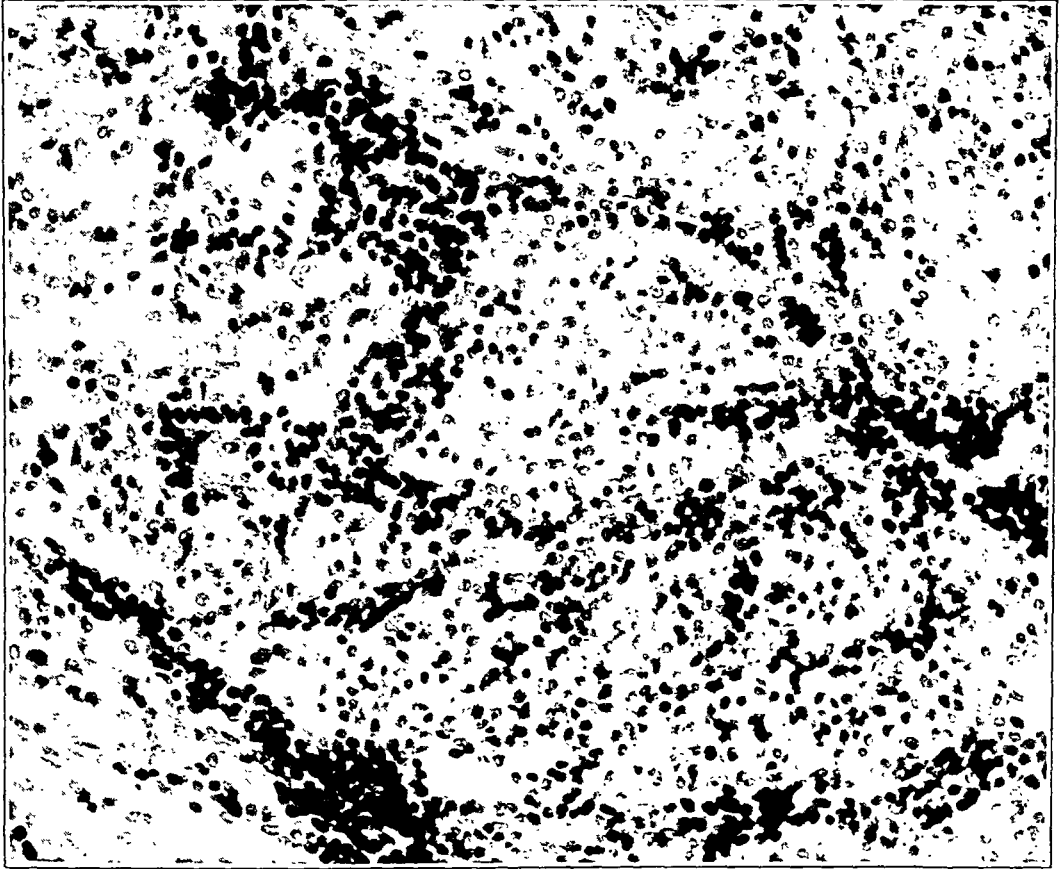


Fig. 2.—Section showing the dense infiltration of the muscular wall of the duodenum with small round cells;  $\times 300$ .

layers could be distinguished. The mucosa and submucosa together accounted for one half to two thirds of the total thickness of the stomach wall.

On neither side of the pylorus was there any definite gross ulceration; however, both areas of mucosa appeared reddish brown, roughened, slightly eroded and slightly pitted. On the stomach side, especially, this eroded surface was covered by a thin, dirty membranous scum easily removed. In no place was the surface depressed.

Microscopic sections were stained with hematoxylin and eosin, as well as by the Ziehl-Neelsen method for tubercle bacilli.

Superficial gross inspection of the sections through the duodenum showed that the entire width of the section stained deeply with the nuclear stain. The mucosal

surface was covered by a thin layer of loose exudate, *débris*, mucus, polymorphonuclear leukocytes and round nuclei. Just beneath this the mucosa was absent over the central portion of the specimen; around the edges it was present, the glands of Brunner being distorted and pushed widely apart. Some of the glands, especially near the periphery, appeared normal, but nearer the center they were undergoing decomposition, their lumina collapsed, the cell outlines indistinct. The whole field around these remaining glands and the space where they were entirely missing were occupied by an intense infiltration of cells—mostly small round cells, but mixed with a fair percentage of polymorphonuclear leukocytes and epithelioid cells. A few eosinophils were to be found scattered here and there.

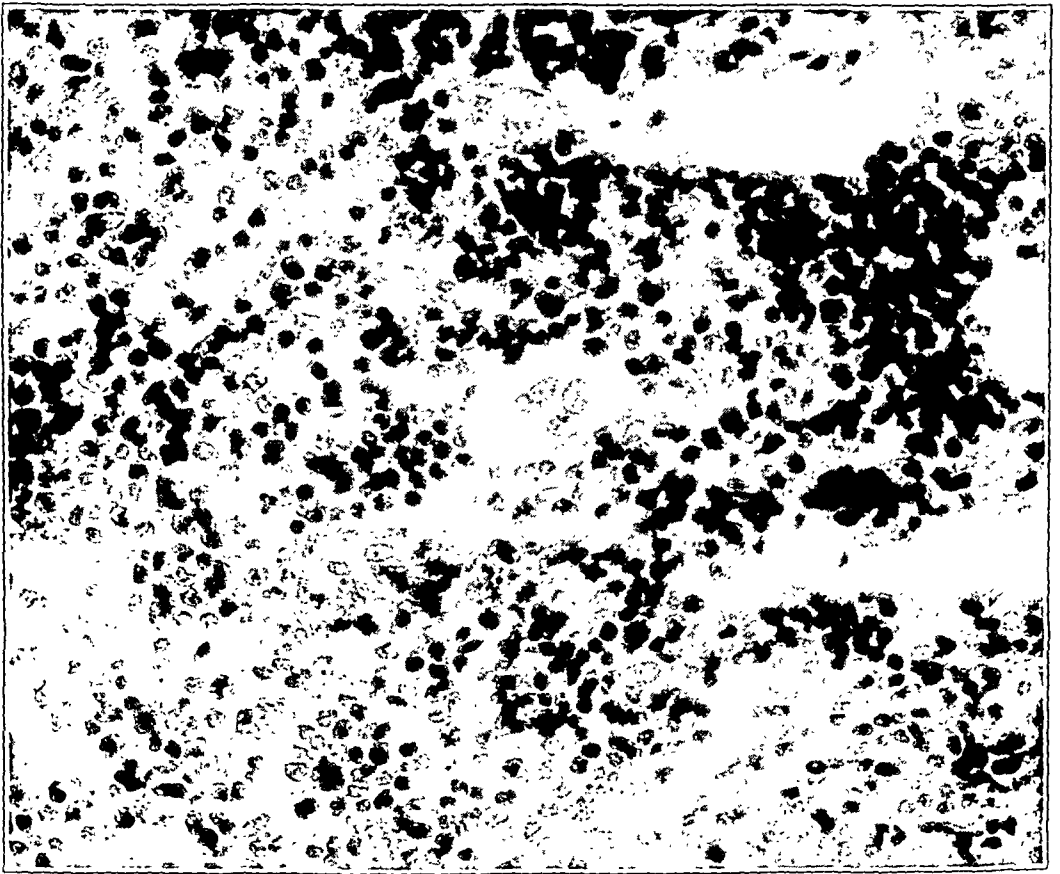


Fig. 3.—Section from the submucosa of the duodenum showing a giant cell surrounded by small round cells and fibroblasts;  $\times 430$ .

Interlacing among these cellular elements was rather profuse fibroblastic hyperplasia with no definite cell pattern. This profuse cellular increase was quite uniform throughout the sections. The infiltration likewise penetrated the muscular layer, even to the serosa. Near the periphery of the area of infiltration, where the muscular layers were still intact, columns of round cells extended along fascial planes between muscle bundles, separating them (fig. 2); while nearer the center of the lesion the round cell infiltration was more intense, crowding out the muscle cells so that where the infiltration was thickest they could be made out only with difficulty or not at all. Mitotic figures were not found. Occasional multinucleated giant cells were present (fig. 3), and after a prolonged search a fairly typical tuberculous lesion was found (fig. 4).

The foregoing process was localized to the duodenal side of the pylorus. Sections made through the stomach, just proximal to the pylorus, showed some similar changes. Here, over an area 2 by 4 cm., on the posterior side of the stomach, the mucosa was missing, being replaced by a diffuse cellular infiltration never so thick nor dense as that seen in the duodenal lesion, but nevertheless made up of similar cellular elements. There was a marked hyperplasia of the lymphoid follicles. The submucosa was several times its usual thickness, the increase being due largely to edema. There were collections of lymphocytes in this edematous submucosa, especially around the blood vessels. At one place in the submucosa, near the pylorus, there was a collection of several typical tubercles, containing from one to three

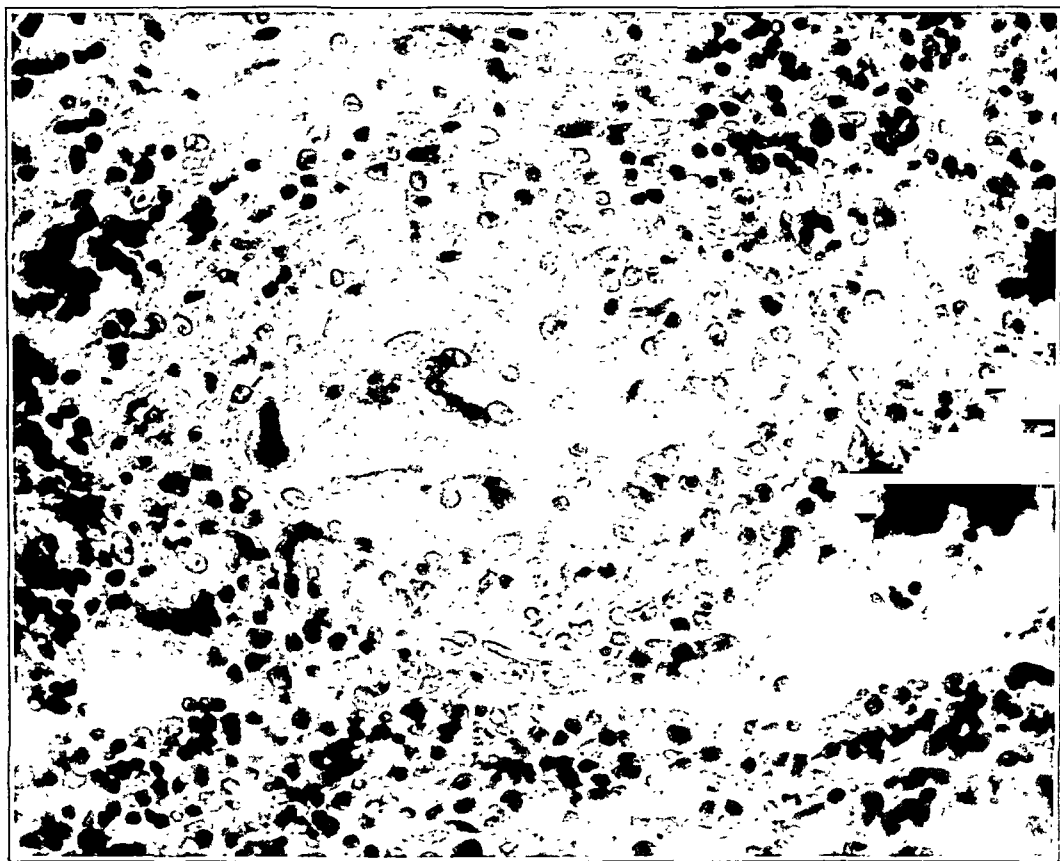


Fig. 4.—Section from the center of the lesion showing characteristic tubercle with giant cell, small round cells and fibroblasts;  $\times 430$ .

giant cells each (fig. 5). There was no sign of caseation in the lesions. The muscularis and serosa were normal.

Many fields in all parts of these sections were examined for tubercle bacilli. None were found.

#### PATHOGENESIS AND PATHOLOGIC ANATOMY OF HYPERPLASTIC INTESTINAL TUBERCULOSIS

The French authors, who made important early studies in this field, divided intestinal tuberculosis into four classes: ulcerative, cicatricial, enteroperitoneal and hyperplastic. The first three are stages in the process



of the destructive, acute tuberculosis so often secondary to advanced pulmonary tuberculosis. They are found in from 25 to 90 per cent of all people dying of pulmonary tuberculosis, but are sometimes found as primary lesions, especially in children. In such lesions the gross and microscopic evidences of tuberculosis are usually easily discerned. To these groups belong by far the larger number of cases of duodenal tuberculosis so far reported. The fourth type, according to the French classification, the hyperplastic form, is proliferative, chronic and much rarer. It is so unusual that it deserves a note of special mention.

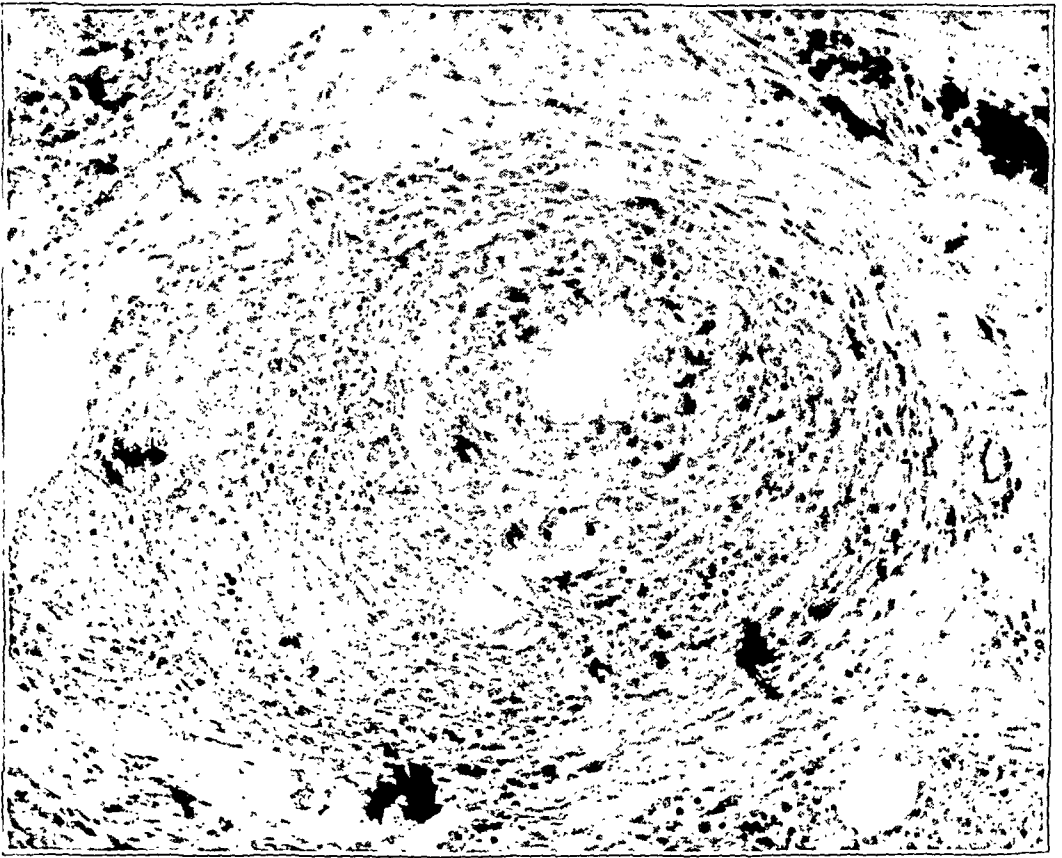


Fig. 5.—Section taken from the wall of the stomach about 1 cm. proximal to the pylorus, showing a typical tuberculous lesion;  $\times$  190.

In most of the cases of hyperplastic intestinal tuberculosis some inactive tuberculosis may be found elsewhere in the body on careful search, but a coexistent active tuberculosis is quite unusual. Indeed, in some cases there may be found no other demonstrable tuberculosis. According to Caird, infection occurs through the blood stream or lymph stream. Authors differ as to sex incidence. Cases have been reported in age groups varying from childhood to old age, although the middle period of life yields the majority of cases.

Excellent descriptions of the pathologic anatomy involved are to be found in the papers of Lartigau, Caird, and Masson and McIndoe. According to these authors, such a proliferation of fibrous tissue occurs that variable, though considerable, annular thickenings of the wall of the bowel occur, the bowel varying from 0.5 to 3 cm. in thickness. The disease is of long standing, and the "chronicity of the disease and its low grade of inflammation are believed to be due either to an attenuated bacillus, or to one of low virulence, elaborating small quantities of exotoxin, sufficient only to produce proliferation, and not necrosis of fibrous tissue. The formation of tumor is the ultimate result" (Masson and McIndoe). The tumor may be freely movable or bound down by adhesions. Clinically and grossly, it may and often does appear exactly like carcinoma; the process has been likened to such hypertrophic and hyperplastic processes as pyloric carcinoma, keloid or lupus. Caird said that "it is this extraordinary hypertrophy which constitutes the leading pathological feature, and also constitutes the leading danger, that of stenosis from the associated longitudinal and circular contraction of the new fibrous tissue," and added, "it is a curious fact that this very attempt to effect a cure by free proliferation should defeat its object and conduce to a fatal issue. Nature is unable to deal with the accident of the situation." Surfaces made by cutting the tissue appear whitish and are firm. The mucous membrane is frequently thrown up into folds or presents papillomatous projections, and there is usually some ulceration of the mucosa at one or more points. The regional lymph glands are often involved. Necrosis and caseation are infrequent, probably because the blood supply to the area is so well preserved. By far the greater number of cases are ileocecal, the number of cases limited to the small bowel being extremely small (according to Masson and McIndoe, only seven have been reported).

The histologic appearance is that of the combined effect of a tuberculous and simple inflammation, presenting an inconstant picture. The mucosa may be intact and the epithelium normal. The glands are pushed wide apart and distorted by a dense lymphoid and epithelioid infiltration in which occasional tubercles may be found. Fibroblasts are very numerous. The infiltration continues into the submucosa, which may be from five to eight times its normal thickness. If tubercles are found they are generally found here and are usually not caseous, but as Lartigau stated, they are "mere aggregations of lymphoid cells in which one or more giant cells may be seen." The muscular layer is thickened by hypertrophy of the muscle fibers, but even more by the dense invasion of lymphoid and epithelioid cells which separates and often destroys the muscle cells. Patches of lymphoid and fibroblastic cells extend even into the subserosa. Summarizing, the dense infiltration of round cells, mixed with fibroblasts and a small number of epithelioid cells and poly-

morphonuclear leukocytes, constitutes the essential feature of the disease; the submucosa is oftenest the site of the densest infiltration. Masson and McIndoe said, "all authors are agreed that the microscopic evidence of tuberculosis is exceedingly atypical and that careful search must be made before tubercles and foci of tuberculous granulation tissue are discovered." Lartigau added, "the typical histologic features of tubercle tissue are often absent; in lieu thereof there may exist a diffuse embryonal cell infiltration, at times capable of simulating sarcoma." This similarity to sarcoma, particularly lymphosarcoma, is repeatedly mentioned in the literature. Tubercle bacilli have seldom been found in the tissues.

#### SYMPTOMATOLOGY

Melchior stated that there are three forms of duodenal tuberculosis, according to the clinical picture: (1) completely symptomless lesions; (2) lesions discovered incidental to tuberculous disease in the rest of the bowel causing symptoms there, and (3) tuberculous ulcers with a symptom picture identical with that of the common variety of duodenal ulcer. Melchior mentioned but does not emphasize a few cases of obstruction of the duodenum due to stricture formation following tuberculous ulcers. By far the greater number of duodenal tuberculous lesions occur in the first part of that organ. Hence symptoms of obstruction or distress from these lesions are those characteristically caused by disease of the first part of the duodenum. In those cases presenting a history like that of common duodenal ulcer, the acidity of the gastric juice (whenever it was mentioned) has been either normal or slightly above the normal. In our case, however, there was no free acid in the gastric content.

Schwatt and Steinbach asserted that the appearance of symptoms of intestinal tuberculosis in patients already suffering from pulmonary tuberculosis is a herald for a fatal termination of the disease in from three to six months. A duodenal tuberculous ulcer in such a patient is more apt to perforate and cause death than ulcers lower down in the bowel. Tuberculous lesions of the duodenum not associated with generalized active tuberculosis are apt to be chronic, and symptoms extend over a period of years. One is apt to wonder whether the patient were not suffering at first from the common form of duodenal ulcer which subsequently became infected with tubercle bacilli from some source, especially since such ulcers often present evidence of recent acute tuberculosis rather than of chronic involvement. The diagnosis of the tuberculous nature of the lesion has seldom been made before operation or autopsy.

The hyperplastic form of intestinal tuberculosis produces, as one would surmise from its pathologic features, a slowly increasing obstruc-

tion with its characteristic symptomatology. Fever is usually absent in this type of tuberculosis.

#### TREATMENT

As was previously stated, diagnosis of duodenal tuberculosis is rarely made before the diseased part is actually under the eye. Whenever feasible, surgical intervention is the treatment of choice. Authorities are one in the opinion that radical excision is to be preferred in cases of hyperplastic tuberculosis. When possible, the same treatment would appear most desirable in isolated tuberculous ulcers or strictures of the duodenum. Lesions of the duodenum cannot, of course, always be resected, and gastro-enterostomy must be done. This treatment has sufficed in some cases for an apparently satisfactory recovery (Blad, Moynihan, Cohen, Fischer). Naturally, surgical operation is not to be considered in patients with generalized advanced tuberculosis.

#### SUMMARY

1. A case of duodenal obstruction due to hyperplastic tuberculosis of the duodenum is presented. The histologic resemblance of this tissue to lymphosarcoma is very striking, and it was only after a careful study of many sections that a typical tuberculous lesion could be found. The presence of tuberculosis elsewhere in the body of course supports the diagnosis.

2. A list of 123 cases of duodenal tuberculosis has been compiled from the literature, and is presented. A good many of the cases may not have been tuberculous. It is not inconceivable that a patient suffering from phthisis, for example, or intestinal tuberculosis, might have in addition a common duodenal ulcer. Some of the cases very likely belong to this category, as neither gross nor microscopic confirmation of the diagnosis of tuberculosis was always recorded. Nevertheless, all the cases reported as duodenal tuberculosis have been included in order to make the list as complete as possible.

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# CYSTIC NODULES OF THE TERMINAL FINGER JOINTS

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BALTIMORE

Nodes of the terminal joints of the fingers have been described as pathologic conditions per se, but have been particularly valued as diagnostic criteria for general ailments. Thus hard knobs of the terminal phalanges, Heberden's nodes, are familiar as evidences of arthritis. On the other hand, soft nodules of the fingers, uratic tophi, are accepted as indications of gout. Obviously, if soft nodules are found in this region that are arthritic rather than gouty in origin, the diagnostic sign becomes inadequate and misleading. It is with such nodules that this paper deals.

In 1802, Heberden<sup>1</sup> called attention to the knobs on the terminal joints of the fingers and indicated his belief that "they have certainly nothing in common with gout." This announcement was followed by a deluge of papers, some of which supported Heberden's theory, while others vehemently denied it.<sup>2</sup> These radical differences of opinion are probably responsible for the numerous studies on the pathologic picture.

In 1881, Charcot,<sup>3</sup> after noting that the "anatomical lesions in this miniature joint-disease (Heberden's nodes) have not yet been described," stated:

The articular cartilages undergo the velvety change; then they disappear, and an eburnated osseous layer is found in their place. The articular surfaces enlarge in all directions, on account of the growth of osteophytes, which almost exactly reproduce in an exaggerated form their shape and normal contours. The pea-like

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From the Department of Orthopedic Surgery, the Johns Hopkins Medical School.

Read before the New York Academy of Medicine, Section of Orthopedic Surgery, Nov. 20, 1931.

1. Heberden, William: *Commentarii de morborum historia et curatione*. London, T. Payne, 1802, chap. 28, p. 130.

2. There is a rather interesting sidelight on this controversy in the copy of Heberden's "Commentaries" at present in the library of the Medical and Chirurgical Faculty of Maryland. This book, a first edition, has apparently passed through many hands and some of the readers have left marginal notes. In the chapter on Rheumatism, where Heberden writes, "The Rheumatism is undoubtedly nearly allied to the gout," some one has written in longhand, "This is undoubtedly false!" Beneath this in another handwriting is written, "I will be damned if it is not!" It is signed "P. J."

3. Charcot, J. M.: *Clinical Lectures on Senile and Chronic Diseases*, London, New Sydenham Society, 1881, p. 197.

enlargements which as Heberden said, are met with in the neighborhood of the second phalangeal joint are nothing but the osseous nodules, which exist normally on the head of the second phalanx at its dorsal aspect; only the size of these nodules is considerably increased by the growth of new layers of bone. There is no trace of sodium urate deposits either in the substance of the articular cartilage or in the soft parts in the neighborhood of the joints.

In 1876, A. B. Garrod,<sup>4</sup> in a clinical description, mentioned soft nodules concerning which he observed that "although these protuberances never give exit to chalky matter, yet in a few cases I have known them to discharge a slightly yellow transparent viscous substance, about the consistence of the white of egg. This has generally been after they have been punctured by the patient."

In 1902, Pribram,<sup>5</sup> describing Heberden's nodes, wrote: "If they are observed from the very beginning, it is noted that they originally have a soft consistency, in some instances actually fluctuate, but that in their development their consistency very soon becomes hard. Usually in spurts, occasionally continuously, they enlarge till they finally reach the size of a pea or larger to the right or left of the terminal joint."

The confusion that attended the studies on these nonosseous nodules is indicated in the description in 1907 by Strangeways<sup>6</sup> of his roentgenologic and pathologic studies. He wrote: "The transparent areas were found on dissection to be erosions of the bone filled with a gelatinous or mucoid looking substance. In advanced cases a characteristic deposit of urates was found. There is good evidence to show that this gelatinous substance may be again transformed into bone. This process is well known in the case of Chronic Gout, but seems to have been overlooked in certain cases which are at present diagnosed as Rheumatoid Arthritis." He differentiated them from Bruce's nodes,<sup>6</sup> the bony deposits on the sides of the phalanges. Later, A. E. Garrod<sup>7</sup> indicated that "sometimes, in addition to the bony enlargement, small translucent cystic swellings are seen upon the postero-lateral aspects of the joints, at the summits of the nodes, and are probably herniae of the synovial membranes."

These cystic nodules of the terminal phalanges are not frequently observed. Since 1920, when, under the stimulus of my chief, Dr. William S. Baer, I began to look for this lesion, I have seen less than

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4. Garrod, A. B.: *A Treatise on Gout and Rheumatic Gout*, ed. 3, London, Longmans, Green & Co., 1876, p. 504.

5. Pribram, Alfred: *Chronischer Gelenkrheumatismus und Osteoarthritis deformans*, Vienna, A. Hölder, 1902, p. 142.

6. Strangeways, T. S. P.: *A Study of Joints from Cases of Rheumatoid Arthritis and Chronic Gout by Means of Skiagrams and Dissection of the Affected Parts*, Bull. Com. Study Spec. Dis., Cambridge 1:93 (Aug.) 1907.

7. Garrod, A. E., in Allbutt and Rolleston: *System of Medicine*, London, The Macmillan Company, 1910, vol. 3, p. 32.

one hundred cases. In fact, only twenty-five patients were seen in whom the masses were sufficiently discrete to permit removal of the deposit. In one of these patients two specimens, and in another three specimens, were obtained, yielding in all twenty-eight specimens available for study.

The condition occurs as a rule in well nourished people over 40. Though men and women are both affected, the predominance of women in this series is notable. Of the twenty-five patients from whom specimens were removed, only two were men. It is particularly interesting to note that in the colored race, which constitutes 19 per cent of the dispensary patients at the Johns Hopkins Hospital, not one instance of these cystic nodules was observed. The cysts were generally found on hands that already presented classic Heberden's nodes. In twenty-one of the patients the hands showed only a single soft nodule at a time. In

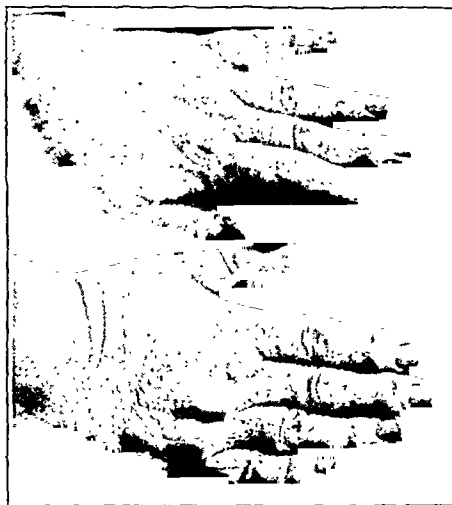


Fig. 1.—The swelling on the dorsoradial side of the distal joint of the left middle finger is soft, while the knobs of the terminal joint of the other fingers are hard classic Heberden's nodes.

each of the other four, two nodules were seen at the same time. The two patients who supplied more than one specimen yielded them at intervals of from six months to one year.

It is noteworthy that most of the patients did not come in complaining of these tumors. Only one came in to find out if she had a cancer on her finger. The cysts were generally recognized in the course of the general physical examination. A few patients complained of continuous pain, and many more spoke of tenderness only on pressure. The condition was found in fourteen persons suffering from an active general osteoarthritis. None of the patients was gouty. I might copy Heberden's words on his nodules, that they "have certainly nothing in common with gout, for they are found in patients who have no experience of that disease."



The cysts appear as soft nodules on the dorsum of the terminal joints of the fingers, to one side or the other of the midline. Two patients showed a nodule on each side of the same finger, and in these there was apparently a connection with the joint cavity, as the compression of one swelling led to an enlargement of the one on the other side of the finger. But these did not resemble accurately the other nodes, which appear as pink to grayish cystic swellings, occasionally translucent, depending on the thickness of the skin covering them. Rarely are they any larger than a pea. On palpation the fluctuant nature is easily determined. Pressure does not obliterate the usual nodule, so that I am led to believe that the sac is not a bursal estuary of the synovial membrane. At any rate, if the pocket began as an outgrowth of the joint lining, the herniation has been sealed off to form an isolated unit. This is quite obvious when the sac is opened. In those instances in which a careful inspection of the



Fig. 2.—The left index finger shows a cystic nodule in a hand that otherwise presents classic Heberden's nodes.

inside of the emptied sac was permitted, it was noted that the lining was a pearly gray, glistening membrane, uniform in smoothness, with no evidence of pocketing. Roentgen examination showed the hypertrophic changes characteristic of Heberden's nodes.

The recognition of these cysts and the differential diagnosis should present no difficulties. Occurring over the distal interphalangeal joints of osteoarthritic hands, often seeming to be classic Heberden's nodes, but proving to be soft on palpation, they are not likely to be confused. In one patient not in this series there was observed an enlargement of the terminal joint surrounding the articulation like a collar; this was multiple and soft but nonfluctuant. On section it proved to be a tumor of the xanthomatous type. The clinical appearance in this instance was quite different from the condition described here. By way of contrast, the gouty tophi, of which but few have come to my attention, were described by Garrod as "apt to be limited to the end-joints of one or

two fingers; [they] are often asymmetrical, and are accompanied by an obvious swelling of the structures around the joints, which gives them a more bulbous and less nodular appearance."

The clinical course of the cystic nodes is quite uniform. In those patients in whom it was found expedient to leave the nodules without surgical intervention, the soft mass became solidified to form a genuine Heberden's node. The lapse of time necessary for this calcification varied from a few weeks to a few months. It is my impression that the ultimate bony node is slightly smaller than the soft tumor at its greatest. On the other hand, when the gelatinous content of the tumor is removed, the sac collapses and heals, to leave a much smaller swelling. A recurrence of the cyst is rarely noted. Generally the enlargement of the finger at this point becomes negligible when the mucoid mass is evacuated.



Fig. 3.—The distal joint of the little finger has yielded a rather large drop of mucoid material. The bony changes are identical with those seen in Heberden's nodes.

Local treatment only will be discussed here. Obviously, if these nodules are local manifestations of a general disease, in all probability osteoarthritis, the systemic condition should receive attention. The local treatment has been found to be simple and effective. The discrete mass is frozen by an ethyl chloride spray. A small transverse incision is made, and while the tissues are still hard pressure is applied on each side of the incision with the back of the knife and a clamp. The contents of the sac pop out as a clear bead. The area is wiped off and a sterile dry dressing is applied. After a few days, the dressing is removed and the wound is found closed with little evidence of scar and without the original swelling. When incision is not feasible, baking gives relief from pain and slight reduction in size. The results of the surgical procedure are uniformly good, and for those patients who complain of the presence of the tumor they are quite gratifying. It is also noteworthy that the pain originally present in the node clears up satisfactorily.

The study of the mucoid material removed from the swellings is interesting. In gross appearance, the bead of semifluid substance expressed from the incised nodule is generally a clear, transparent homogeneous mass, gelatinous in character and sufficiently viscous under the lowered temperature of the ethyl chloride spray to retain its spherical form. As the bead rises in temperature to approximate body heat, it becomes limpid, so that it flows with a mucilaginous consistency. When it is allowed to dry on a glass slide, its translucence becomes lost to form a white, slightly opaque film that becomes quite adherent to the glass.

Microscopic examinations of the unstained smear have shown an amorphous mucoid, occasionally stringy material. Methylene blue (methylthionine chloride, U. S. P.) Wilson's and hematoxylin-eosin stains of the smear fail to demonstrate any cellular structure. One bead that was successfully embedded in celloidin and stained with hematoxylin and eosin showed, when sectioned, an almost homogeneous mass with several areas of mild differences in refraction that suggested the wall of a broken-down cell. No nuclear tissue was seen. The material was mildly eosinophilic. None of the specimens showed crystals or fatty globules.

Bacteriologic investigations consisted of making cultures from seventeen of the specimens on agar slants and in broth mediums. No growth was obtained in any of the tubes.

Chemical studies were made of several specimens. As mentioned before, no crystalline structure could be found in any of the microscopic examinations. Sudan III and osmic acid tests gave negative results for fat. The Folin test indicated that there was no uric acid. One finger yielded enough material for a microchemical quantitative analysis of the calcium content. It is noteworthy that the cystic contents showed 98 mg. of calcium per hundred cubic centimeters, although the blood of the patient contained only 10.2 mg. per hundred cubic centimeters. Unfortunately, there was not enough material left for a quantitative examination for phosphorus, which is probably of greater importance in osteoarthritic chemical studies.

In reviewing the studies on the cystic nodules of the terminal phalanges, it is apparent that this condition is found only in patients with osteoarthritis. Analysis of the incidence and distribution of the soft masses shows a close conformity to the distribution of Heberden's nodes with regard to age, sex, type and color of patient. When allowed to follow an unmolested course, these nodules always become hardened to form knobs that cannot be differentiated from Heberden's nodes.

It is therefore safe to express the belief that they represent a stage in the formation of the "digitorum nodi" described by Heberden. The failure to find any trace of urates or of uric acid emphasizes the inde-

pendence of the condition from gout. The negative bacteriologic observations are worthy of consideration, particularly by those who consider all nonspecific arthritis the result of focal infection. It is hoped that a sufficient amount of the gelatinous material can be accumulated to permit a more complete study of what appears to be an intermediary step in the process of calcification.

#### SUMMARY

1. Soft nodules are found on the terminal joints of the fingers that differ radically from the tophi in gout.
2. The incidence of these nodules and their clinical course indicate that they are a preosseous stage of Heberden's nodes.
3. Studies of the contents of the nodules show a gelatinous material high in calcium content.
4. The absence of uric acid and urates dissociates this condition from gout.
5. A simple and efficient method of treating the swelling is reported.

# EXPERIMENTAL PRODUCTION OF INFLAMMATORY AND SUPPURATIVE CONDITIONS OF THE LUNG

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The etiology of pulmonary suppuration and allied conditions has been the subject during the last few years of a number of intensive investigations. A number of clinical and experimental studies have appeared in the literature. The difficulty of producing inflammatory and suppurative processes in animals by the bronchial route has long been recognized; on the other hand, such processes are easily initiated by way of the circulation by the introduction of infected material into the veins, as has been demonstrated by Cutler and others. Pulmonary abscesses following tonsillectomies—the postoperative abscess—stimulated much of this work. Such an abscess forms the greater number of those occurring in the lung, and, if they form as the result of aspiration, should have quite a different pathogenesis from those caused by the introduction of infectious material into the veins.

Abscesses following tonsillectomy constitute almost 50 per cent of all postoperative abscesses of the lung. If the embolic theory is to be accepted, this complication should follow both local and general anesthesia in about the same ratio. Lyman, however, reported 20,000 tonsillectomies performed under general anesthesia without abscess formation as a complication, and Hedblom made a similar report from the Mayo Clinic. On the other hand, many cases of abscess of the lung have followed operations performed under local anesthesia. The greatest number of pulmonary complications occur after operations in the presence of inflammation, on movable viscera with numerous venous plexuses. The late onset of symptoms, from ten to twenty days after the operation, lends support to the embolic theory. Theoretically, if due to aspiration of septic material during the operations, they should develop much earlier.

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An abridgment of this paper was read by Ascoli before the Royal Academy of Medicine of Rome.

Gebele, Gottstein, Mikulicz and Ranzi, and more recently Capelle and de Quervain, accepted and defended the embolic theory of the development of pulmonary suppuration.

Clinical proofs are far from satisfactory. In general, it may be accepted that the pulmonary complications following operations on the mouth or pharynx occur when the pharyngeal and laryngeal reflexes are lessened or abolished. Interference with the reflexes may occur under both general and local anesthesia. In Italy, operations on the tonsils are nearly always performed under local anesthesia, and abscesses of the lung following such operations are practically unknown. The gross anatomic appearance of the pulmonary lesion in such cases is not like that usually seen when septic emboli reach the lung. The operations that are most frequently followed by pulmonary suppuration are not those that are complicated by a suppurative thrombophlebitis. This has been pointed out by one of us in a statistical paper. However, Cutler's experiments, as originally made and modified, have been repeated and confirmed many times.

A great number of experimental data are at hand, which show how difficult it is to produce suppuration by the introduction of infected material by way of the bronchial tree. Schlueter and Weidlein introduced far down into the bronchial tree of fifteen dogs pieces of diseased tonsils from patients, foreign bodies and various micro-organisms. They did not produce a single abscess. Similar experiments had already been made by Cutler with the same results. Joannides introduced infected foreign bodies directly into the lung through the thoracic wall. These became encapsulated by a thick membrane. Abscess formation did not occur. Joannides also introduced into the bronchial tree blood infected with cultures of staphylococcus.

Scarff recorded a long series of experiments performed by himself. All were unsuccessful. They may be grouped as follows:

1. Bronchoscopic Methods
  - (a) Simple destruction of parenchyma of the lung
  - (b) Introduction into a secondary bronchus of pledgets of cotton soaked in cultures of staphylococcus
  - (c) Introduction into a secondary bronchus of a vegetable foreign body
2. Transpleural Methods
  - (a) Destruction of parenchyma of the lung with boiling water.
  - (b) Injection of staphylococcus and streptococci
  - (c) a + b
  - (d) a + b + foreign body

Many similar experiments are recorded by others. The results were negative, or a rapidly progressive pneumonitis, terminating fatally, developed. Few have succeeded experimentally in producing abscess of the lung. Crowe and Scarff introduced deeply into the bronchial tree

through the bronchoscope pledgets of cotton soaked in scrapings from the teeth of patients with pyorrhea, or produced a suppurative frontal sinusitis in dogs with the same organism. They have been able in this way to produce abscesses of the lung, some becoming chronic. Allen was able to produce abscesses experimentally in a small percentage of cases by insufflating into the trachea of dogs pus from a chronic pulmonary abscess in a man. He believes that the pus must be insufflated while warm, because the spirochetes to which he attaches etiologic significance lose their pathogenicity when cold. Allen stated that he succeeded in 100 per cent of his attempts, when after insufflation he tied the bronchus. Scarff also attaches much significance to the pulmonary collapse which follows closure of the bronchus. According to Joannides, pulmonary suppuration can be caused by insufflation into the bronchial tree of blood mixed with septic material. Harkavy, Smith, Kline, Olch and Ballou have caused suppuration by simple ligation of the pulmonary artery.

The impression is gathered after reading the literature that experiments in which emboli were used, whether with the technic employed by Cutler or modified by others, yield a high percentage of positive results. The results following placing of septic material in the bronchial tree seem at times to be accidental, and not the necessary consequences of the altered conditions provided by the experiment. A regular and definite series of controls is also often wanting. Only those experiments in which a suppurative sinusitis was produced by Crowe and Scarff seem to give a higher percentage of positive results, occurring more regularly than those obtained by other experimenters using many methods.

The experiments presented in this paper may be grouped as follows:

1. Production of pleural adhesions either by direct suture of the lung to the pleural wall, or by extrapleural packing followed by endotracheal insufflation of a culture of staphylococcus from a chronic abscess of the lung.
2. Insufflation into the trachea of various simple and anaerobic cultures from chronic pulmonary abscesses and scrapings from the teeth of a patient with pyorrhea alveolaris, followed immediately by closure of the inferior right bronchus by means of a skin clip applied from without.
3. Formation of a fistula between the esophagus and trachea.

#### EXPERIMENTAL WORK

Rabbits were used in all the experiments. In series 1, all experimental results were negative. Two and one-half cubic centimeters of a 24 hour old broth culture was insufflated into the trachea. Such a small

quantity will not produce a diffuse inflammation of the lung. This occurs only when a large amount of the culture is used.

In series 2, the animals died soon after the introduction of cultures into the trachea, which were made from the scrapings from the teeth of a patient with pyorrhea alveolaris. At postmortem examination the blocked lobe appeared red and hard like liver, and on microscopic examination the changes of pneumonitis were found. A serofibrinous pleurisy, with adhesions about the collapsed lobe, was also found. The remaining lobes of both lungs were quite normal.

Less rapid death, but with the same anatomic findings, has been noted when cultures of the same kind as in series 1 have been used in other rabbits. Attempts have been made to cause milder inflammatory changes with the idea of causing an abscess in the lung. Such attempts were not successful. Quantities of 1 cc. and less from five to seven day old and older cultures of staphylococcus and from twelve to fourteen day old cultures of anaerobes were used. Pneumonitis of the occluded lobe developed in all the animals, and they died rapidly.

There were ten animals in series 3. One died two days after operation of mediastinitis, in one the fistula closed and in the remaining eight diffuse lobular pneumonitis developed, ending in the formation of cavities, varying in size. Three of these animals were fed exclusively on liquid sterilized foods. These lived longer than any of the others.

The following were the objects of this investigation:

1. To determine if fixing the lung to the thoracic wall would so reduce the resistance of the portion of the lung so fixed, as the result of inspiratory trauma and interfering with coughing, as to allow the growth of pathogenic organisms which otherwise would be destroyed or ejected.

2. To investigate the significance of the closed cavity in the bronchial tree and the protective power of the normal lung in experimental animals by which pulmonary abscesses are prevented after the insufflation of septic material into the bronchial tree.

3. To investigate the pathogenic power of mildly septic material injected repeatedly and over a long time into the bronchial tree.

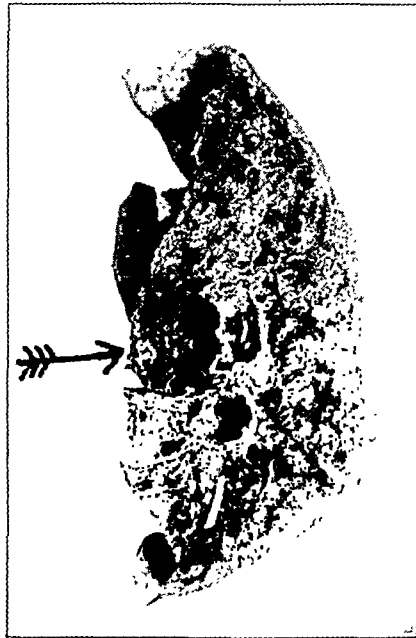
4. To determine if suppuration in the lung can be produced by the bronchial route.

A number of reasons have been shown why it is difficult to produce pneumonitis and suppuration of the lung by the bronchial route. Among these are the different pathogenicity which the organisms used develop in man and animals and the high protective power against infection of the normal lung. This is probably due to the rich blood supply of the normal lung and to the ease with which germs may be removed



from the bronchial mucosa by the cilia and coughing. The horizontal position of the bronchial tree in animals probably increases the effectiveness of this mechanism.

If a portion of the lung is fastened to the thoracic wall by adhesions, coughing is interfered with, and ejection of material from the normal and pathologic cavities is impaired. Moreover, the walls of the alveoli of the fixed portion are separated by the respiratory movements which are more forcible than normal. Inspiratory trauma thus produced lessens the resistance of the lung and favors the development of organisms. Such changes have apparently not been sufficient in these experiments.



Centrally situated cavity found filled with pus and necrotic tissues. The animal (rabbit 9, series 3) died ten days after operation.

From series 2, one may conclude that the power of ejecting organisms is the most effective protection afforded the lung. In ten experiments, in all of which pneumonitis developed in the occluded lobe, not even a mild inflammatory process was noted in the remaining intact ones.

The efficiency of a closed cavity in increasing the virulence of organisms should be emphasized. As it has already been pointed out, it has been impossible to produce milder inflammatory lesions with an occluded lobe. Experiments have been planned in which organisms from the animal's own mouth would be used.

In the third series of experiments evidence is brought forth to show that septic materials left a certain time in contact with the mucosa of

the bronchial tree and the alveolar epithelium will cause inflammatory changes in the lung, terminating in suppuration; in eight of ten animals pneumonitis developed. Those living the longest developed cavities of various sizes. Why two experiments failed has already been stated. Animals in series 3, kept in ordinary cages, with a straw litter and fed on common vegetables, died from four to five days after the operation, that is, from two to three days after feeding was started; while those kept in surroundings where they could find nothing to gnaw and fed on scanty, liquid, sterilized food lived from seven to eight days after feeding was started.

The operative wounds healed *per primam*. The fistula was made with one layer of a continuous perforating suture; notwithstanding this, in but one case did an inflammatory process develop in the cellular tissues of the neck and mediastinum. This indicates that the organisms responsible for the changes in the lungs were but slightly pathogenic for the rabbit. When the animals have special care, such as the aforementioned, the saprophytes of the mouth and pharynx are probably the only ones to be considered as related to the infection of the lung. We have attempted to give bacteriologic proof of this. This is not positive enough, however. It must be emphasized that in these cases no foreign bodies—at least not solid ones—could be aspirated.

We conclude that experimentally the most important factor in the production of abscess of the lung is the inability of the animal to rid itself of particles of moderately septic material deposited on the bronchial and alveolar epithelium. This inability is noted when a fistula is made between the esophagus and trachea. The normal respiratory mechanism is seriously interfered with. Cough is impaired, for the bronchial tree is no longer completely closed at the beginning of the act, and the material gaining access to the bronchial tree through the fistula can no longer be expelled.

It seems worthy of note that one animal lived almost eight days in apparently good condition, although it had a fistula measuring 3 to 4 mm. in width. Liquids had probably been aspirated for several days when the abscess, terminating in death, developed. In this case, at least, pneumonitis did not follow immediately the aspiration of septic material.

The results of the experiments here recorded support in a way those of Crowe and Scarff—the development of an abscess of the lung due to the aspiration into the bronchial tree of pus from a sinusitis, due to the placing in the trachea of scrapings from a case of pyorrhea. In this experiment organisms of relatively high pathogenicity are kept for some time in contact with the bronchial and alveolar mucous membrane.

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# ETIOLOGY OF GALLSTONES

## II. ANALYSIS OF DUCT BILE FROM DISEASED LIVERS

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In a former paper<sup>1</sup> it was shown that the cholesterol in bile is held in solution in a more or less stable complex with the different bile salts, and that any lowering of the bile salt-cholesterol ratio below a certain point would bring about a precipitation of the cholesterol. It was also demonstrated that while the normal dog's gallbladder absorbed neither in appreciable amounts, the abnormal gallbladder absorbed bile salts and thus lowered the ability of the bile to hold cholesterol in solution, and brought about crystallization.

It was then mentioned as theoretically possible that the liver itself might be a factor, in that bile might be excreted with a very low bile salt-cholesterol ratio, and that this might even be low enough to bring about precipitation of cholesterol. While it is difficult to see how the excretion of solid undissolved cholesterol would be possible, nevertheless, if the bile excreted was near or at the critical point where precipitation begins, it would make it much easier for the gallbladder by its action to disturb the ratio a little more and cause stone formation. The following observations suggest that the liver may at times play a very important rôle.

### OBSERVATIONS

*Analysis of Dog's Liver Bile.*—The first suggestion of the importance of the liver came to our notice when a dog was encountered accidentally who had an extreme cirrhosis of the liver. The liver was of the atrophic type, being quite light yellow, greasy and nodular to an extreme degree, grossly a typical hobnail liver in every respect. The dog's abdomen had been opened for another purpose, but when the condition of the liver was noted, the common duct was cannulized and enough bile secured for analysis. It was quite watery and lighter in color than normal. Analysis of the bile gave a total solid content of 4.25 per cent, 70 mg. of cholesterol

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From the Department of Surgery of the University of Chicago. This work was done in part under a grant from the Douglas Smith Foundation.

1. Andrews, E.; Schoenheimer, R., and Hrdina, L. Studies on the Etiology of Gallstones: I. Chemical Factors and the Rôle of the Gallbladder, *Arch. Surg.* **25**:796 (Oct.) 1932.

per hundred cubic centimeters, but a bile acid content by the method of Schmidt and Dart of only 42 mg. per hundred cubic centimeters. The normal bile salt content of liver bile is from 0.6 to 1.4 per cent. This was most surprising, as according to our theory there was not enough bile acid to dissolve the cholesterol, and still it was there in solution and not in emulsion form. While the total solids were rather low, there was still a large amount of solid material in the bile unaccounted for by the usual amounts of the normal biliary constituents, and we were led to conclude that this other substance must be holding the cholesterol in solution. Unfortunately, it was impossible in this case to pursue the matter further on account of lack of material.

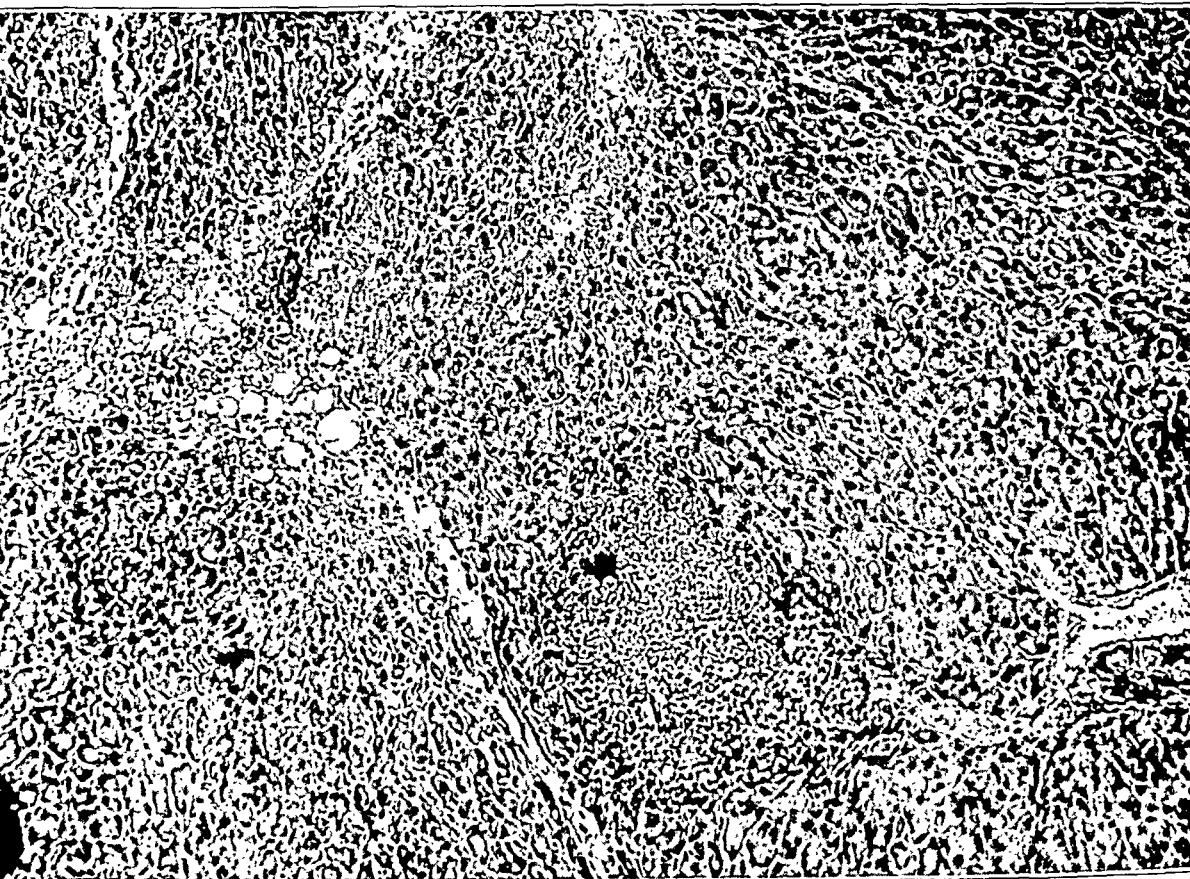


Fig. 1.—Liver from the dog, showing cirrhosis of a peculiar type; reduced from a magnification of  $\times 130$ .

The histologic findings in this dog's liver were as follows (fig. 1): The liver lobules were separated and partly split by a great increase in fibrous tissue and spread widely apart. In the periportal tissues there were many round cells and some fat cells. The Kupffer cells of the periphery were much enlarged and filled with a brownish-yellow pigment. In the liver cells but a small amount of pigment was found. In a few places in the liver lobules there were circumscribed necrotic areas, with infiltration of round cells and leukocytes. In the finer bile ducts and blood vessels there were no changes whatsoever. A diagnosis was made of cirrhosis of the liver in an advanced stage, of a type unknown in man.

The following observations were made on the livers of patients whose cases are reported here.

CASE 1.—A. I., aged 53, had suffered from recurrent attacks of cholecystitis of great severity for many years, although jaundice had not been found. Roentgenograms revealed a negative shadow of a large number of gallstones, and the edge of the liver was palpable about 3 cm. below the costal border. At operation, the gallbladder was found to be thickened especially at its neck, and twenty-five faceted gallstones of uniform size were removed. The stump of the cystic duct was opened before it was ligated, and a few cubic centimeters of liver bile was aspirated. This liver bile was unusually light in color and quite milky and opaque, due to the presence of very large numbers of cholesterol crystals. The gallbladder bile was of normal color, but it was also definitely cloudy with precipitated cholesterol. The bile salt content of the liver bile was only 86 mg. per hundred cubic centimeters in both this patient and the dog, being but a small fraction of the normal findings.

It is clear in this case, therefore, that precipitation of cholesterol not only in the gallbladder but in the common duct was due to the fact that not enough bile acids were present to hold it in solution, and the finding of cholesterol crystals in duct bile seems indicative of the fact that the liver itself may play a rôle in the formation of gallstones.

CASE 2.—Mrs. E. C., aged 35, entered the hospital with the usual symptoms of diabetes-pruritus, polyuria and polydipsia of nine years' duration. The diabetes had been recognized previously. It was of a mild grade. However, for the last four months the patient had had repeated attacks of acute gallbladder colic, and on examination it was noted that a large, definitely hard, rounded edge of the liver could be palpated about four fingerbreadths below the costal border. The presence of beginning biliary cirrhosis was suspected, and its effect on the diabetes was taken into consideration. It was advised by her attending physician, Dr. Russell Wilder, that a cholecystectomy be performed and that a prolonged bile drainage be instituted as well.

With the patient under ethylene anesthesia, the abdomen was opened; the liver was found to be markedly enlarged, and its edge was rounded and very hard, containing numerous white scars. The gallbladder was easily removed, although it was buried in old adhesions which, however, separated very easily. The cystic duct was clamped and a cholecystectomy performed, and through the stump of the cystic duct as large a catheter as could be inserted was fitted snugly up into the common duct. The patient's convalescence was perfectly uneventful, and she was able to take a full diet on the third postoperative day. For nineteen days all the bile was drained through the tube, and the stools were acholic throughout this period. At that time the tube was removed, and the bile drainage stopped completely and suddenly on the same day. During this period of nineteen days, the patient's bile was analyzed daily for its bile salt and cholesterol content. During this period numerous feeding experiments were carried on, results of which are plotted in figure 2. The results of these experiments may be summarized as follows:

During the first twelve days, the patient complained bitterly of nausea and loss of appetite on the days on which she did not receive a dose of bile salts by mouth. They seemed to be remarkably effective in replacing the normal bile as an adjunct to digestion. After about two weeks by some compensatory mechanism, the patient no longer suffered from the lack of bile salts to anything like the degree that was

apparent during the first two weeks. During the first two weeks, attempts to administer a placebo which the patient was told was bile salt did not help to ward off the nausea which came on after each meal. Throughout much of this period the patient was on the routine diabetic management and was receiving a diet rather rich in fats. The substitution of a high protein diet did not remove the nausea and indigestion on the days when bile salts were not administered.

Two different types of bile acids were used in doses of 0.5 Gm. by mouth. They were given in a powdered form in several large capsules. Dehydrocholic acid and also desoxycholic acid were used in these experiments. They were both very well tolerated. These bile acids were unconjugated, and it has always been assumed that there was never an excretion of unconjugated bile acids in the bile and that

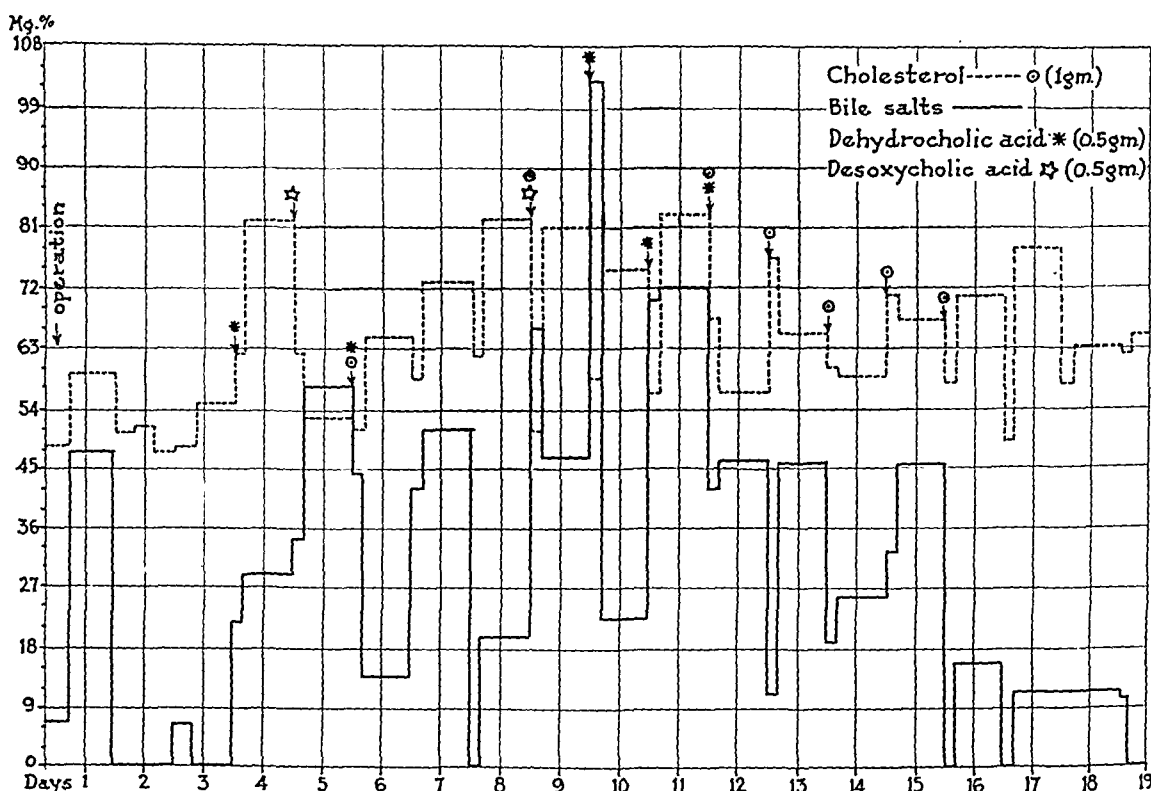


Fig. 2.—Chart showing the cholesterol and bile acid content of the bile under various conditions in case 2.

combination of them with glycocholl or taurine always occurred in the liver. In our experiments during the first week of the operation, feeding unconjugated bile acids produced only a slight elevation in the rate of excretion of conjugated bile acids, while during the second week, after the liver had a chance to recover from the anesthetic poisoning, feedings of the same amount of bile acids in the unconjugated form caused a considerably larger excretion of the conjugated bile acid. The excretion of the amounts of bile acid fed was slower than reported by Wisner and Whipple,<sup>2</sup> taking two or three days instead of from twelve to twenty-four hours, but the acid could all be accounted for in the bile, in the second series of feedings, after the effect of the ether was over.

2. Wisner, F. P., and Whipple, G. H.: Variations in the Output of Bile Salts and Pigments During 24 Hour Periods, *Am. J. Physiol.* 60:119, 1922.

In the classic studies of Whipple<sup>3</sup> on this subject it was found that there is a regular circulation of bile salts from the liver to the intestine and back again by the blood stream. Any excess produced by feeding was promptly eliminated. Of course, in the presence of a bile fistula with its consequent interruption of the enterohepatic circulation, one would have expected that the elimination would be more complete and rapid.

The most striking fact in our experiments was the extremely small quantities of bile salt found in the bile at any time. Even after feeding bile acids in significant amounts, the concentration in the bile never rose to more than a small fraction of the normal level. In the majority of the thirty-nine analyses, the bile salt concentration was actually below that of cholesterol. According to the theory previously published by us, it takes about thirteen times the volume of bile salts to hold the cholesterol in solution, and therefore one would have expected to find this bile containing cholesterol crystals which, however, was not the case in any of the specimens. More striking still was the fact that in seven of our specimens we could get absolutely no bile acid reaction whatsoever by the method of amino-nitrogen determination (Schmidt and Dart<sup>4</sup>), and we were at a loss to explain

TABLE 1.—*Data in Case 3\**

Days After Operation	Total Solids	Calcium, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.
1.....	1.65	3.6	4.7
2.....	1.07	3.1	11.3
3.....	1.93	12.5	32.9
4.....	2.00	19.8	31.5
5.....	2.07	8.1	60.7
6.....	2.45	7.3	101.6
7.....	2.46	7.0	90.9
8.....	2.42	8.0	87.3
9.....	2.12	7.4	100.0

\* Bile salt content of bile by the aminonitrogen method was 0 in all specimens.

what it was that held the cholesterol in solution. The total solids in the bile in this case averaged quite within normal levels (from 2 to 4 per cent), and in the almost total absence of bile salts which make up about two thirds of the total solids in normal bile, it was again obvious that there was present a large amount of some unknown substance which had the power to hold cholesterol in solution. Unfortunately, the left-over bile, after preparing the samples for analysis, had been thrown away and no further studies were possible.

CASE 3.—Mr. J. D., aged 73, complained of acute attacks of gallstone colic during two of which he had been jaundiced. An operation was performed in which a stone in the common duct was removed, a tube inserted into the duct and bile analysis made daily for ten days. The specimens for the first four days contained very small amounts of cholesterol, which rapidly mounted to normal figures and remained so during the period of observation (table 1). The astonishing fact was that in this case not a single one of the daily specimens contained any bile salts whatsoever by the method of Schmidt and Dart, although the bile throughout the experiment was quite clear and contained no cholesterol crystals. In this case also the total solids were about normal. This was the third observation of this same

3. Whipple, G. H.: The Origin and Significance of the Constituents of the Bile, *Physiol. Rev.* **2**:440, 1922.

4. Schmidt, C. L., and Dart, A. E.: The Estimation of Bile Acids in the Bile, *J. Biol. Chem.* **45**:415, 1920.



phenomenon, and again we were compelled to fall back on the same assumption that there might have been an excretion of uncombined bile acids in the bile which held the cholesterol in solution. Unfortunately, the original specimens in this case also were lost and no further chemical studies could be made.

The patient died of bile peritonitis on the tenth day, and at autopsy the liver weighed 1,550 Gm. and was not grossly enlarged. There was a considerable increase in the periportal connective tissue, and in some places there was a marked round cell infiltration. The liver cells took the nuclear stain well, and in some parts there was a deposit of a yellow granular pigment. The terminal bile ducts were slightly dilated

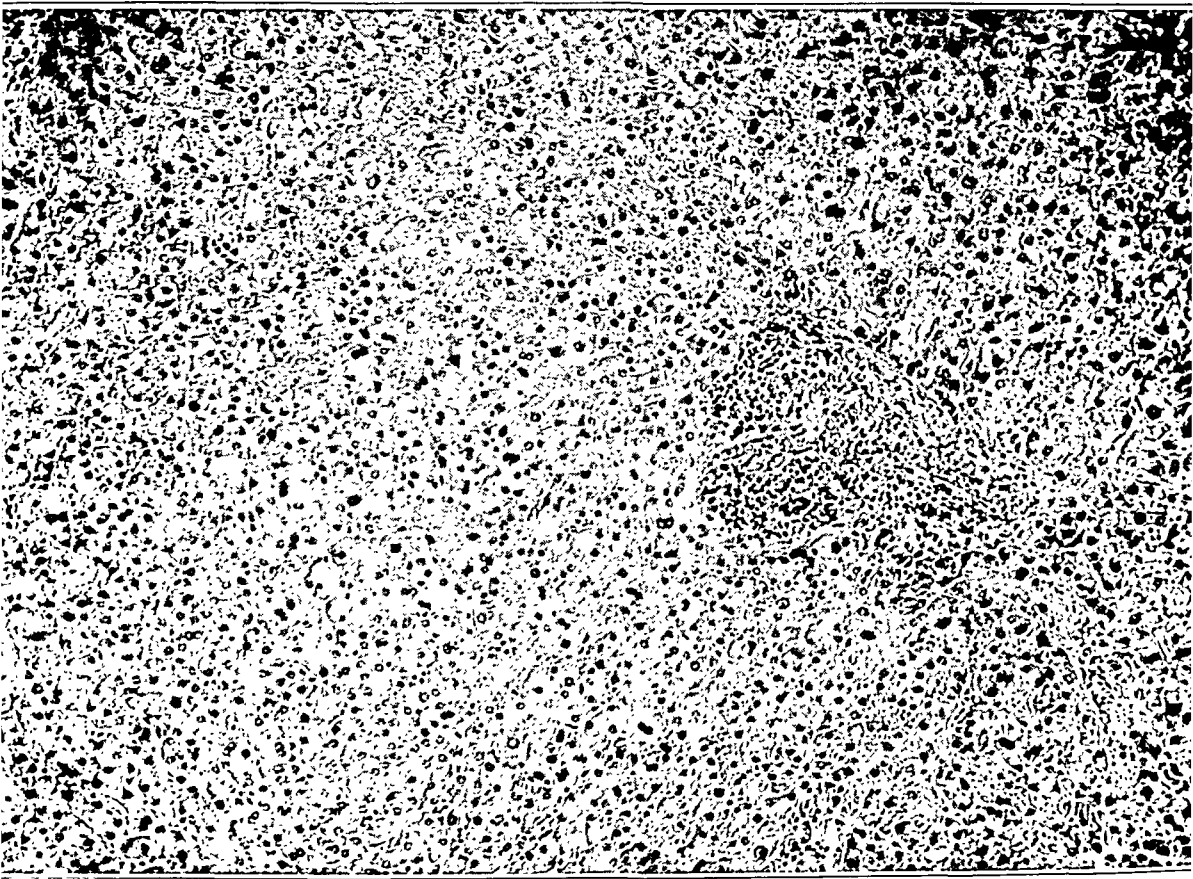


Fig. 3 (case 3).—Liver from patient J. D., showing round cell infiltration and beginning cirrhosis; reduced from a magnification of  $\times 130$ .

but the epithelium was not changed. A diagnosis of beginning biliary cirrhosis was made (fig. 3).

CASE 4.—Mrs. I. M., aged 35, about two years before the present examination had had a cholecystectomy with injury to the common duct. This had been repaired, and become strictured later; an attack of cholangitis had occurred, and finally, another common duct repair was made and a T-tube inserted. Therefore, it is clear that during the preceding two years she had had either a fistula, jaundice or active liver infection covering a period of several months in all.

Daily specimens of bile were secured for forty days after the operation, until the tube was withdrawn. Most of this time part of the bile was passing into the bowel, so that our specimens were not complete as in the other cases. Daily analy-

sis of this bile revealed the astonishing fact that not once during the entire period were there any bile salts present by the aminonitrogen method (table 2). For the first few days after operation, the flow from the tube was light in color and scanty, as one would expect after the relief of obstructive jaundice. From then until the end of the experiment, it was of normal appearance. The cholesterol content remained at an unusually low level for nearly three weeks after which it rose to fairly normal levels. Here again the total solids were nearly normal in amount. Again the problem arose of how in the latter period of the experiment when the cholesterol content of the bile was about 100 mg. per hundred cubic centimeters it was held in solution in the absence of conjugated bile acids.

In this case the excess bile after analysis was pooled and kept on ice. There was left over after pooling the remaining specimens of bile 800 cc., which on drying yielded 18.5 Gm. of dry residue. This residue contained but 0.51 mg. of

TABLE 2.—Data in Case 4\*

Days After Operation	Total Solids, per Cent	Calcium, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.	Days After Operation	Total Solids, per Cent	Calcium, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.
1	....	4.8	9.2	21	1.55	3.8	28.5
2	1.06	3.0	8.4	22	1.55	4.0	50.7
3	1.46	3.4	7.2	23	1.89	5.1	53.3
4	1.15	3.3	7.5	24	1.57	4.7	55.2
5	1.84	2.6	10.5	25	1.90	4.8	56.1
6	2.43	3.5	6.3	26	1.92	3.7	64.5
7	1.44	3.5	8.5	27	1.66	4.8	51.7
8	1.14	3.5	10.4	28	1.60	4.7	47.8
9	1.42	3.0	7.4	29	1.60	3.9	41.1
10	1.10	4.3	7.3	30	1.42	3.8	43.5
11	1.40	2.4	4.3	31	1.51	5.3	55.0
12	1.15	1.5	11.6	32	1.72	6.0	62.8
13	1.42	3.0	5.8	33	2.19	6.8	77.4
14	1.51	3.8	13.5	34	2.33	7.1	70.5
15	1.05	3.8	10.3	35	2.40	6.6	54.1
16	1.57	3.8	7.5	36	2.46	7.2	71.2
17	1.39	3.9	9.4	37	2.09	6.6	78.9
18	1.46	4.1	22.9	38	2.14	6.2	90.2
19	1.55	4.1	31.5	39	2.62	6.7	104.8
20	1.69	4.2	55.1				

\* Bile salt content of bile by the aminonitrogen method was 0 in all specimens.

combined aminonitrogen, representing but about 1 Gm. of combined bile salts. There were isolated from this residue by preparative chemical methods described elsewhere<sup>5</sup> 0.49 Gm. of desoxycholic acid and 2.2 Gm. of cholic acid. As in the methods used about half of the substances were lost in the purification, it is safe to assume that the original content was about twice as much. Thus there was about five times as much uncombined as combined bile acid in this bile. As cholesterol may be held in addition compounds with these simple bile acids as well as the combined ones, it is clear what factors accounted for its solubility, in this case at least.

#### COMMENT

In one case, therefore, it was positively proved that the liver excreted unconjugated bile acids in considerable amounts, and we believe that good presumptive evidence is offered that this is the explanation of the fact that cholesterol was held in solution in the others. In each of the cases it was clear that there was damage to the liver. One liver was

5. Schoenheimer, R., and Andrews, E.: To be published.

obviously cirrhotic, one gave definite histologic evidence, a third was grossly enlarged with thick rounded edges, and another had a history of recent jaundice, which always brings about definite pathologic changes in the parenchyma of the liver. The proof therefore seems quite clear that the damaged liver may at least partially lose the power to combine simple bile acids with glycocholic or taurine. Whether the normal liver also secretes simple bile acids in small amounts cannot be told with our present methods of chemical analysis of bile acids. In order to separate the two types quantitatively, there is such a large loss in purifying the different fractions (about 50 per cent) that one can detect the simple bile acids only if there is a large amount of them present. However, the unanimity of the literature on the subject renders it very doubtful. The important point is that in very many previous analyses of bile by competent chemists, the total solid content was fully accounted for by the uncombined bile acids and the other known biliary constituents.

The literature on the excretion of bile acids by the liver in health and disease is voluminous and need not be reviewed here. It was summarized by Whipple<sup>2</sup> in 1922 and Walters<sup>6</sup> more recently. It may be summed up briefly by stating that minimal amounts of liver damage cause a profound lowering of the bile acid content of the bile. The mechanism of excretion is such a delicate one that infinitesimal doses of liver poisons which produce no clinical symptoms whatsoever will bring about a marked lowering of the biliary excretion of bile salts.<sup>7</sup> Walters<sup>8</sup> also showed that there is a minimal bile salt excretion after the relief of obstructive jaundice.

One very important result of these observations is to throw grave doubts on nearly all the previous experimental work on bile acid excretion. The method which has been used almost universally has been that of Schmidt and Dart,<sup>4</sup> that is the determination of the amino-nitrogen by the Van Slyke<sup>9</sup> technic. Of course, this gives accurate results only if the premise on which it was founded is true, that is that all bile acids are in the conjugated form. If, as we have shown, in liver disease there is an excretion of unconjugated bile acids, these would not be found by the Schmidt and Dart method. The work of Walters<sup>10</sup> and his associates was done with the quantitative Petten-

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6. Walters, W.: *Obstructive Jaundice*, Rochester, Minn., Mayo Foundation Publications, 1931.

7. Whipple, G. H.: *Bile Salt Metabolism*, J. Biol. Chem. **59**:623, 1924.

8. Walters, W.; Greene, C. H., and Frederickson, C. H.: *Composition of the Bile Following the Relief of Biliary Obstruction*, Ann. Surg. **91**:686, 1931.

9. Van Slyke, D. R.: *The Quantitative Estimation of Aliphatic Amino Groups*, J. Biol. Chem. **12**:275, 1912.

10. Greene, C. H.; Frederickson, C. H., and Walters, W.: *The Composition of the Bile Following the Relief of Biliary Obstruction*, J. Clin. Investigation **9**:295, 1930.

koffer method of Aldrich.<sup>11</sup> This, while it is subject to the criticism that it is not specific enough for use in the bile as the fatty acids and other Pettenkoffer-reacting material cannot be completely removed, would at least yield a more general idea of the bile-salt content than one which ignores large amounts of uncombined bile acids as the amino-nitrogen method does.

For studies on gallbladder bile such as those previously reported by us, the aminonitrogen method is quite valid. Hydrolysis of bile acids into unconjugated forms never takes place in the body as far as is known. The only hydrolyzing enzyme reported in the body capable of splitting up this compound is that isolated by Grassmann and Kali Pada Basu from the kidney.<sup>12</sup> Newman<sup>13</sup> found that gallbladder bile could be kept for several weeks without the slightest hydrolysis of the conjugated bile acids.

It is clear from the foregoing facts that if, as we have reported,<sup>1</sup> the bile salt-cholesterol ratio in bile is an important factor in gallstone formation, the rôle of the liver may be an important one. After liver damage the cholesterol content of the bile may be reduced, but in other cases it attains levels comparable to those found in normal bile. Even if the maximum possible content of unconjugated bile acids is taken into consideration as a solvent for cholesterol, the total bile acids are often very low, being below (one case) and very near (four cases) to the critical point at which cholesterol is precipitated.

#### CONCLUSIONS

1. One case is reported in which it was definitely proved that there was a large excretion of unconjugated bile acids in the bile.
2. Three other cases were found in which this phenomenon was presumptively present as on no other assumption could one account for the solubility of large amounts of cholesterol in the bile and its high total solid content.
3. All these patients had definite liver disease of some type.
4. One of the patients had a liver bile containing cholesterol crystals.
5. The rôle of the liver in secreting bile of such low bile salt-cholesterol ratio that it is at or near the critical level for precipitation is suggested.

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11. Aldrich, M., and Bledsoe, M. S.: Studies in the Metabolism of Bile, *J. Biol. Chem.* **77**:519, 1928.

12. Grassmann, W., and Basu, Kali Pada: Ueber die enzymatische Spaltbarkeit geparter Gallensäuren, *Ztschr. f. physiol. Chem.* **198**:247, 1931.

13. Newman, C. E.: Beiträge zum Studium des Gallenniederschlags und Gallensteinbildung, *Beitr. z. path. Anat. u. z. allg. Path.* **86**:187, 1931.

# SACROCOCCYGEAL TERATOMAS

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Since the review of the literature and the report of a case by one of us (Dr. Hansmann), which coupled certain gross as well as histologic features of the tumor concerned with residual structures of the neurenteric canal, reports of composite tumors immediately anterior to the sacrum have from time to time appeared in the medical literature. A review of these cases has convinced us that the idea of histogenesis is still vague in the reported cases. If the interpretation is correct that no inconsiderable number of these retrorectal tumors arise from remnants of the neurenteric canal, this information would be important in the study of the clinical cases preliminary to the therapeutic removal of the aberrant tissue. We have recently had another patient with a rather unusual retrorectal tumor. The nature of the tumor, the excellent result from surgical removal and the apparent need for a reiteration of the most likely histogenesis have suggested this communication.

## REPORT OF A CASE

*Clinical History.*—A white American girl, 1 month old, was brought to the hospital on Oct. 2, 1930, with a tumor at the lower end of the spine. The tumor had been present since birth and had doubled in size. The mass extended downward from the buttocks and tapered to a blunt point (fig. 1). It was not continuous with the sacrum or the coccyx. Several bony masses were felt in the tumor (fig. 2).

The mass extended anterior to the sacrum and to the coccyx, but its upper limit could not be accurately determined. Certain areas were distinctly cystic.

*Roentgenographic Findings.*—A tumor estimated to be 13 by 14 cm. was noted, which contained many rudimentary bones. No sacral defect could be determined.

*Operative Report.*—Excision was done on Oct. 9, 1930. A large mass was encountered, which extended well anterior to the sacrum. During the dissection a well formed bowel was found intimately applied to the tumor. So perfect was this part of the intestines that the question of whether or not the abdomen had been opened was raised. A decision of this question was made when a somewhat thickened pelvic peritoneum was found intact above the tumor. The tumor was easily freed from the surrounding structures, except in the region of the sacrum and of the coccyx. Here the tumor was attached by tissue of cartilaginous consistency, but no defect in the sacrum was noted.

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*Pathologic Report.*—A mass 15 by 10 cm., which had attached to it an elliptic piece of wrinkled skin 10 by 7 cm., was submitted for examination (fig. 3). The mass contained tissues of various morphologic configurations and appearances. In general, there were solid and cystic portions. On one surface there was well

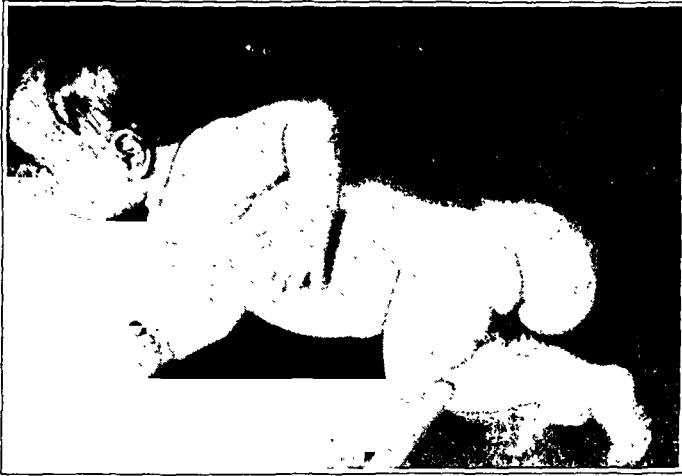


Fig. 1.—Gross configuration of the tumor.

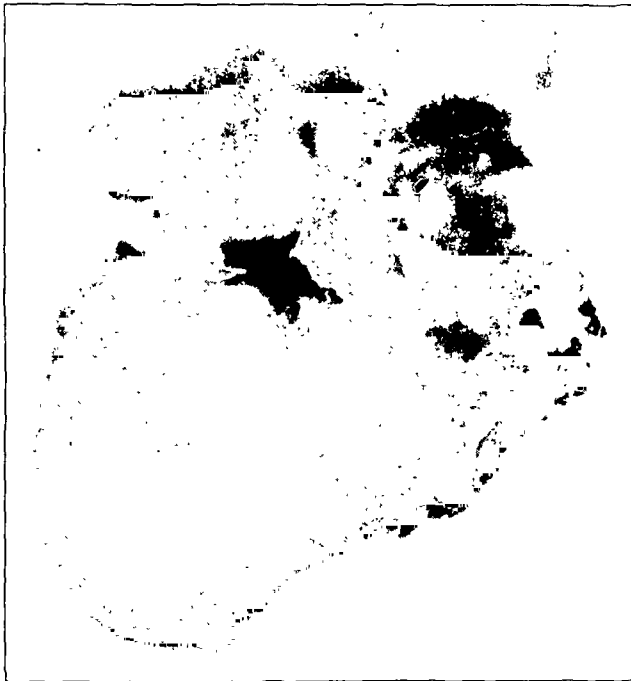


Fig. 2.—Roentgenogram of bone structures in the tumor.

formed intestine. The lumen was at times obliterated. One of these obliterations formed an appendix-like structure. Between obliterations mucocoeles had formed. There was a total of 30 cm. of patent intestine, including mucocoeles but exclusive of obliterations.



Fig. 3.—The removed tumor showing configuration of cysts and of intestine.



Fig. 4.—The removed tumor showing a profile resembling an infant's head.

The solid portion on profile had the configuration of a child's head (fig. 4). This point of view was taken to orient the reader on the gross and microscopic description of this part of the tumor mass. The occipital portion was reddish gray and resembled nerve tissue. Histologic section revealed almost pure glial tissue (fig. 5). Deep in this tissue were the bone structures. They were resected. Vertebral structures that contained nerve tissue resembling the cord were noted.

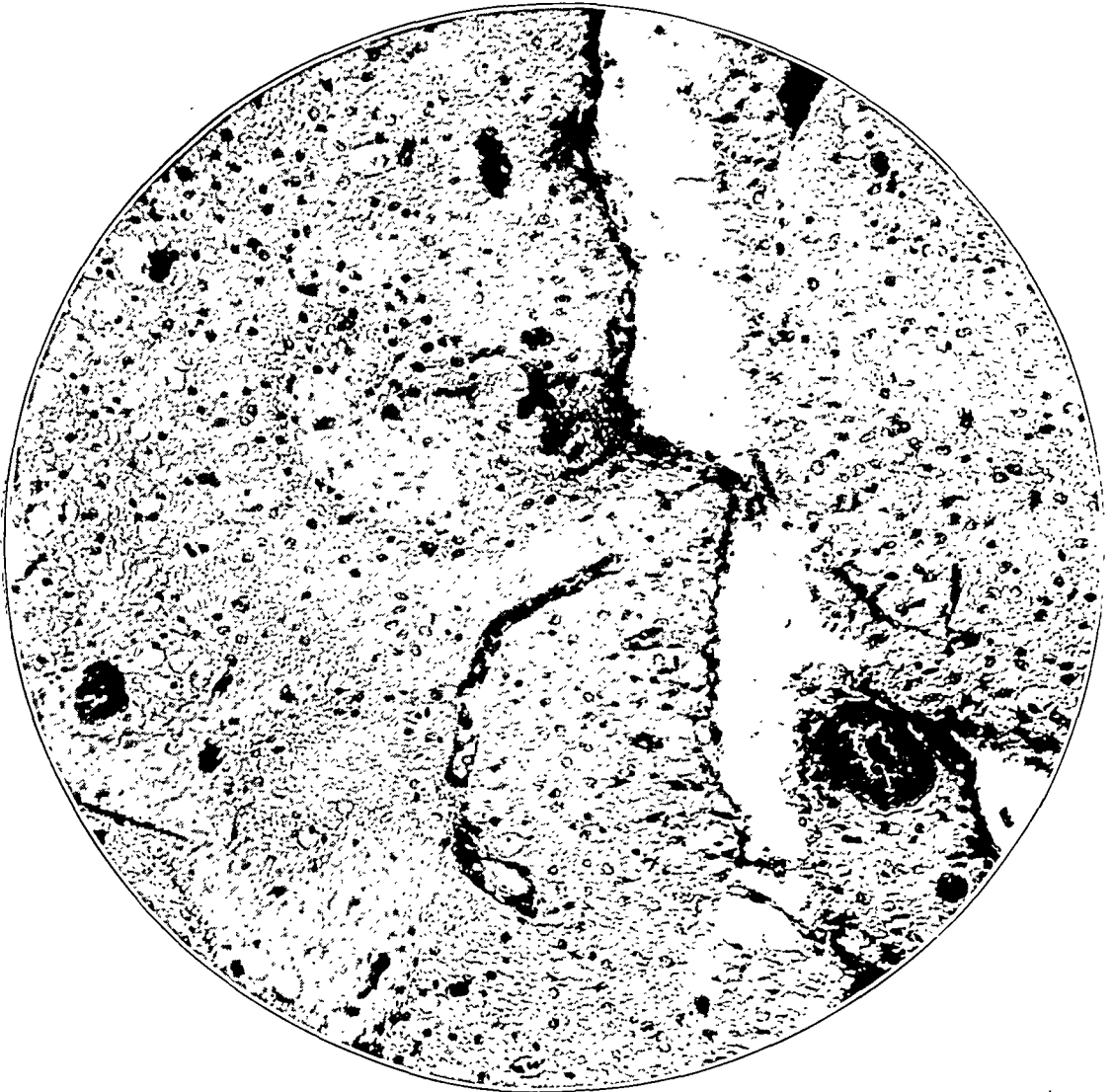


Fig. 5—Solid glial tissue;  $\times 130$ .

It was further noted that tissue resembling nerves emerged from between these bony structures. The adherent soft tissue was macerated, which left behind many poorly formed bones. There was one long bone, 4 cm. in length, that abutted a flared, flat bone which was interpreted to be the ilium. This flat bone in turn articulated with fused vertebrae that were interpreted to be an attempted formation of a sacrum. Nothing could be said of the identity of the remaining fourteen pieces of bone. The protuberance that on profile appeared to be the nose of a child was a mucocoele. The regions that were comparable to the temples had dermoid



inclusions, but nothing comparable to a rudimentary ear could be made out. Small bits of cartilage, small accumulations of lymphoid tissue, well formed nerves and pacinian corpuscles were found in this tissue.

The intestinal portion resembled the large bowel throughout. The stroma supporting the epithelial cells and the configuration of the individual cells, as well as the marked secretion of mucus, were all characteristic of mucosa of the colon (fig. 6).

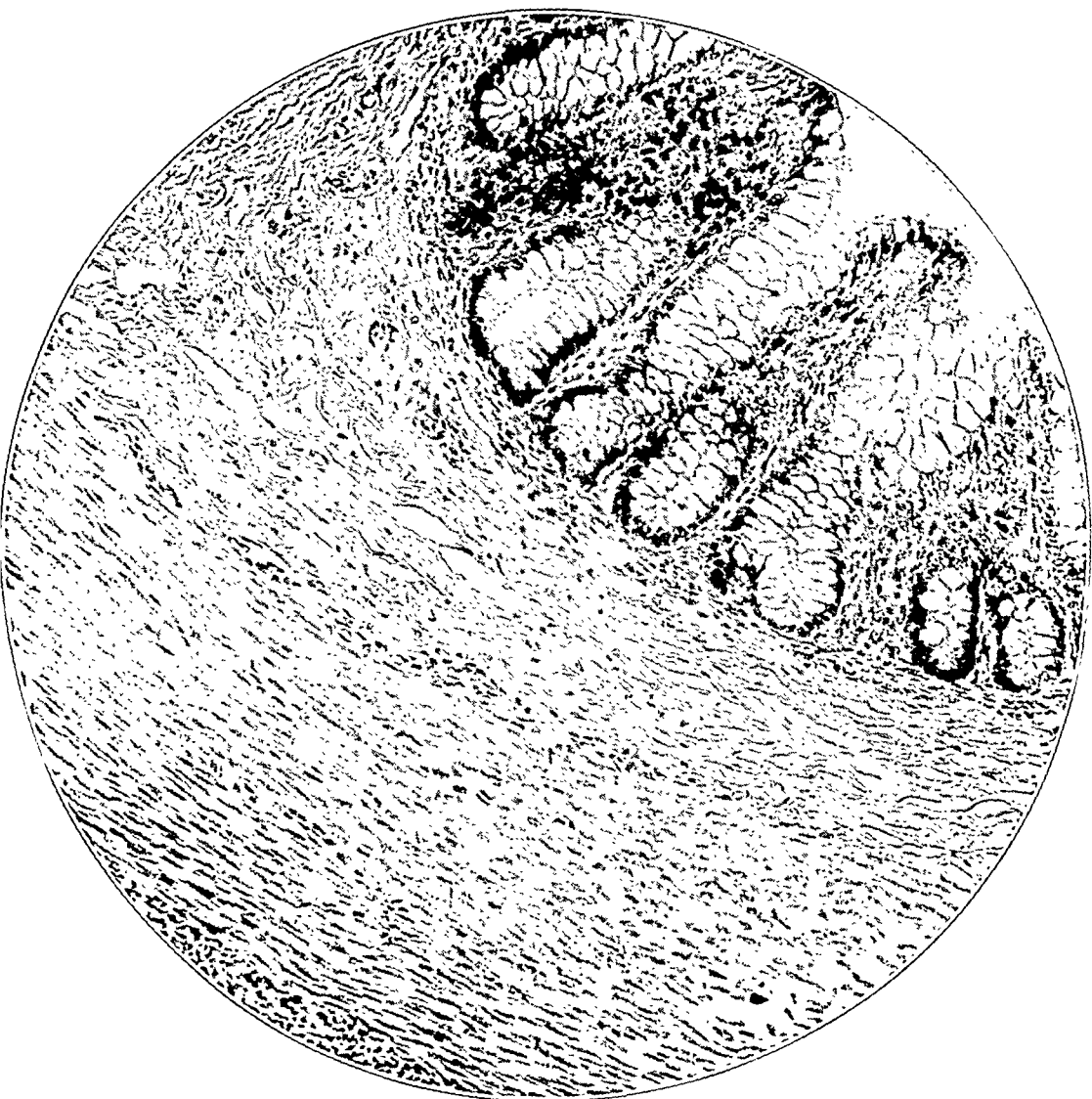


Fig. 6—Intestinal wall;  $\times 130$ .

The large cysts were lined by flattened cells, which in places were in tuftlike arrangement, resembling the tufts of the choroid plexus (fig. 7). Small nests of glia cells and fibrils were found immediately beneath the lining of this cyst. There were two large cysts which measured approximately 5 cm. each in diameter. They were both filled with a serous fluid. There were numerous smaller cysts which contained serous, sebaceous or mucoid material. Their walls were lined by flattened epithelium, mucus-secreting epithelium or stratified squamous epithelium.

*Subsequent Course.*—Following operation, a superficial infection of the wound developed, associated with a slight elevation of temperature. Both promptly subsided. The patient was discharged on Oct. 22, 1930. The wound had closed, and the patient appeared well, and has remained well during the fifteen months since her discharge.

Cases reported from 1924 to 1930 are summarized in the accompanying table. No explanation can be offered for the preponderance of females. The early development of these tumors is fairly definite proof of their relationship to embryologic processes. Whether the tumor reaches to the heels, into the abdomen or laterally into the buttock, the origin is always retrorectal. The attachment to the rectum is, however, seldom intimate. When attachment is intimate, it is usually

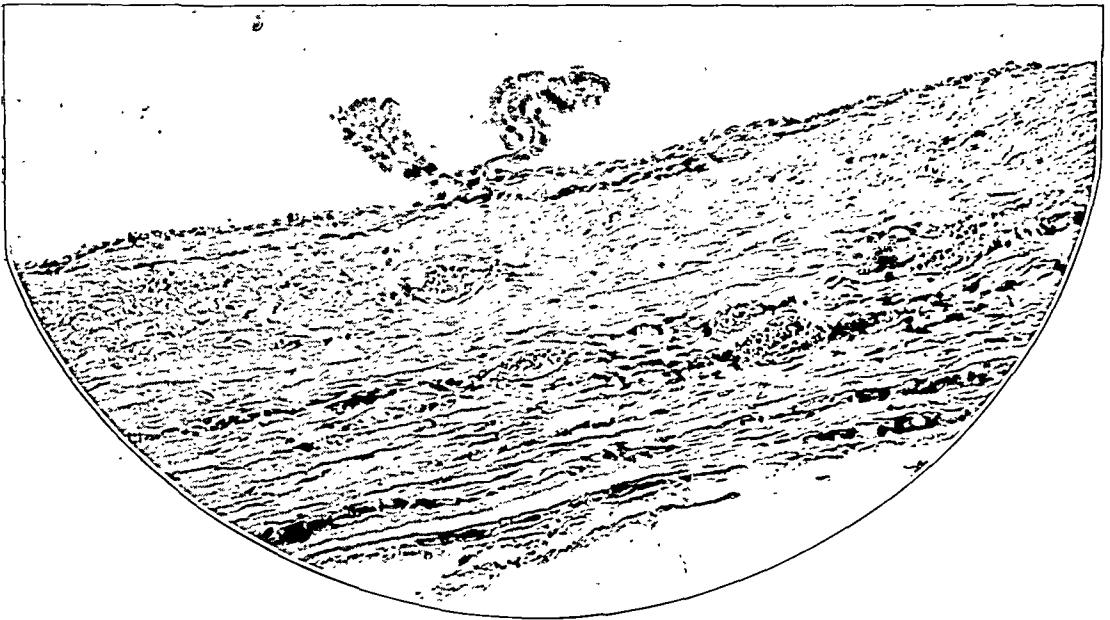


Fig. 7.—Lining of cyst wall with a tuft resembling choroid plexus;  $\times 130$ .

to the sacrum or coccyx or to both. The presence of a sacral defect is suggested in a number of the case reports but not pointedly considered. Definite proof of an origin in the neurenteric canal may therefore have been overlooked.

The histogenesis of these tumors is usually considered to be the independent development of a blastomere during segmentation of the ovum or the development of a misplaced ovum. In view of the constant position of the tumors, it is difficult to accept this explanation, which would seem to involve an assumption of random or haphazard location. Disorderly growth of tissue in the presacral region much later in fetal life would seem to be a more likely cause. The embryologic structures occurring in this region, in the hindgut, in the proctodeal membrane and in the neurenteric canal are sufficient on this basis to account for

*Cases of Sacrococcygeal Teratomas as Reported, 1924-1930*

Refer- ence	Year	Sex	Age	Dura- tion (Approx.)	Diameter, Cm.	Loca- tion	Sacral Defect	Histogenesis	Histology	Removed	History
8	1924	F	43	30 years	20	Retro- rectal	No	0	Cyst with ectodermal and endodermal epithelium	Yes	Recurred twice; well
18	1924	F	3 days	3 days	10?	Retro- rectal	?	Monogerminal implant	Bone, cartilage, nerve tissue, mucus secreting and transitional epithelium	No	Died
4	1924	F	20	2 months	10	Retro- rectal	?	0	Columnar and stratified epithelium, nerve tissue	Yes	Died
20	1924	F	60	?	20	Retro- rectal	Yes	Blastomere	Hair—Wilms' papilla .....	Attempted	Died
14	1924	M	1	1 month	15	Retro- rectal	Yes	0	Glia, epithelium, ependyma.....	Yes	Died
11	1926	F	1 month	1 month	6	Retro- rectal	Yes	Neurenteric canal	Ependyma, intestinal and squamous epithelium, cartilage, glia	No	Died
12	1925	?	1 month?	1 month	10	Retro- rectal	No	0	Large bowel, nerve tissue, cartilage...	Yes	Well
16	1925	M	4½	2 weeks	6	Retro- rectal	No	0	Muscle, nerve, epithelium, cartilage....	Attempted	Died
3	1926	F	8 months fetus	.....	25	Retro- rectal	?	0	Columnar and stratified epithelium, muscle, bone, nerve tissue	.....	Macerated
13	1927	F	1 day	1 day	20	Retro- rectal	?	0	Squamous epithelium, nerve tissue, cartilage	Yes	Well
10	1928	F	1 month	1 month	?	Retro- rectal	?	Blastomere	Nerve tissue, glandular epithelium, cartilage, muscle	Yes	?
		M	1 month	1 month	12	Retro- rectal	?	Blastomere	Nerve tissue, glandular epithelium, cartilage, muscle	Yes	?
		F	1 month	1 month	16	Retro- rectal	No	Blastomere	Nerve tissue, glandular epithelium, cartilage, muscle	Yes	?
6	1929	F	3 days	3 days	11	Retro- rectal	?	Blastomere or inclusion of 2d ovum	Glands, cartilage .....	No	Died
1	1929	F	2 months	2 months	10	Retro- rectal	?	Blastomere	Bone, intestine .....	Yes	Died
17	1929	F	19 months	19 months	6	Retro- rectal	?	Blastomere	Intestine, glands, transitional epithelium	Yes	Well
		F	5 weeks	5 weeks	20	Retro- rectal	?	Blastomere	Stratified epithelium, glia tissue.....	Yes	Well
		F	1	1 year	15	Retro- rectal	Yes	Blastomere	Fat, glia cells, mucus secreting cells...	Yes	Well
		M	6 months	6 months	20	Retro- rectal	?	Blastomere	Stratified and glandular epithelium, glia tissue	Yes	Well
9	1930	M	2	2 years	10	Retro- rectal	?	0	Muscle, cartilage, glandular epithelium	Yes	?
7	1930	F	31	31 years	5	Retro- rectal	?	Misplaced ova	Intestinal glandular squamous epithelium	Yes	Recurred, metastasized?
2	1930	F	21 months	21 months	11	Retro- rectal	Yes	.....	Sweat gland, intestinal mucosa, nerve tissue, bone	Yes	Well
15	1930	F	18 days	18 days	35	Retro- rectal	?	0	Gross bone .....	Yes	Well
19	1930	M	3	2 months	5	Retro- rectal	Yes?	0	Nerve cartilage, fat, muscle, tissue.....	No	Died
5	1930	F	1 day	1 day	10	Retro- rectal	?	Cong. remnant	Cartilage, fibrous tissue, squamous epithelium	Yes	Well

the varying types of tissue occurring in these tumors. The normal biologic stimuli to this region may be responsible for the development of bone, as in the case reported, in which the osseous formation suggested the development of a pelvis. The division of these tumors into teratoid tumors and teratoma should be understood to indicate the degree of development of organs in tumors with the same histogenic basis.

The rapid rate of growth which parallels that of the infant should not be taken as evidence of malignancy. The degree of cell differentiation, however, is important in consideration of malignancy. The gross and microscopic evidence of mature tissue formation throughout is thoroughly reliable information on which to base an opinion of the benign nature of the tumor. A benign tumor may be indicated clinically by evidences of the presence of adult tissue, such as muscle twitchings, peristalsis or the demonstration of bone. In the cases reviewed, in which one or more of these findings were present, the tumor was in each instance benign.

the mortality continues high. In order to increase the knowledge of this serious and baffling disease, all available data should be analyzed from every point of view, and since the pathologic and clinical pictures present such wide variations there must be a detailed examination of the individual groups to determine where improvement is possible. Before I embark on an analysis of the different types, certain points applicable to all cases will be set forth.

#### INCIDENCE AND PATHOLOGY

*Incidence of Types of Obstruction.*—In a consideration of the three hundred and thirty-five cases of obstruction from all causes, certain interesting points as to incidence and pathology deserve comment. The first is the relative frequency of the different types of obstruction, which is shown graphically in chart 1.

TABLE 2.—*Figures from Other Clinics*

Author	Year of Report	Number of Cases	Mortality, Per Cent
Miller: Ann. Surg. 89:91, 1929.....	1929	343	61
Brill: Ann. Surg. 89:541, 1929.....	1929	124	36
Tuttle: Boston M. & S. J. 192:791, 1925	1925	150	50
Souttar: Brit. M. J. 2:1,000, 1925.....	1925	3064	32*
Braun and Wortmann: Der Darmverschluss, Berlin, Julius Springer, 1924..	1924	379	39

\* Including strangulated external hernias, 26 per cent.

It will be observed that strangulated external hernia is the etiologic factor in almost one half of the total number of cases. Obstructions from neoplasms are responsible for about one tenth of the cases. Bands and adhesions are the cause of another large group; intussusceptions and volvuli come next, and the remaining cases are in the rarer groups.

*Distribution by Sex and Age.*—This series shows as usual a preponderance of cases in males (two hundred and sixteen males and one hundred and nineteen females).

Chart 2, which shows the ages of the patients with various types of obstruction, brings out certain interesting points. Obstructions from congenital anomalies and from intussusceptions occurred for the most part in infancy and early childhood. Obstructions arising from bands and adhesions in patients not previously operated on showed two definite peaks, one in the second and third decades of life and another in old age, middle life being relatively free; this is a striking finding, but may be merely a coincidence in this small group. Bands and adhesions occurring either early or late after operation are found for the most part in young adults or in those of middle age, corresponding to the period of greatest frequency of operations. Mesenteric thromboses and other circulatory lesions reach their peak in old age, although cases occur

as early as the third decade of life. Obstructions from neoplasms, as might be expected, reach their peak in old age. In the group of strangulated external hernias, while all ages were represented, a striking peak occurred in the fifth and sixth decades; and while there was no actual peak in early childhood, it is interesting to note that except

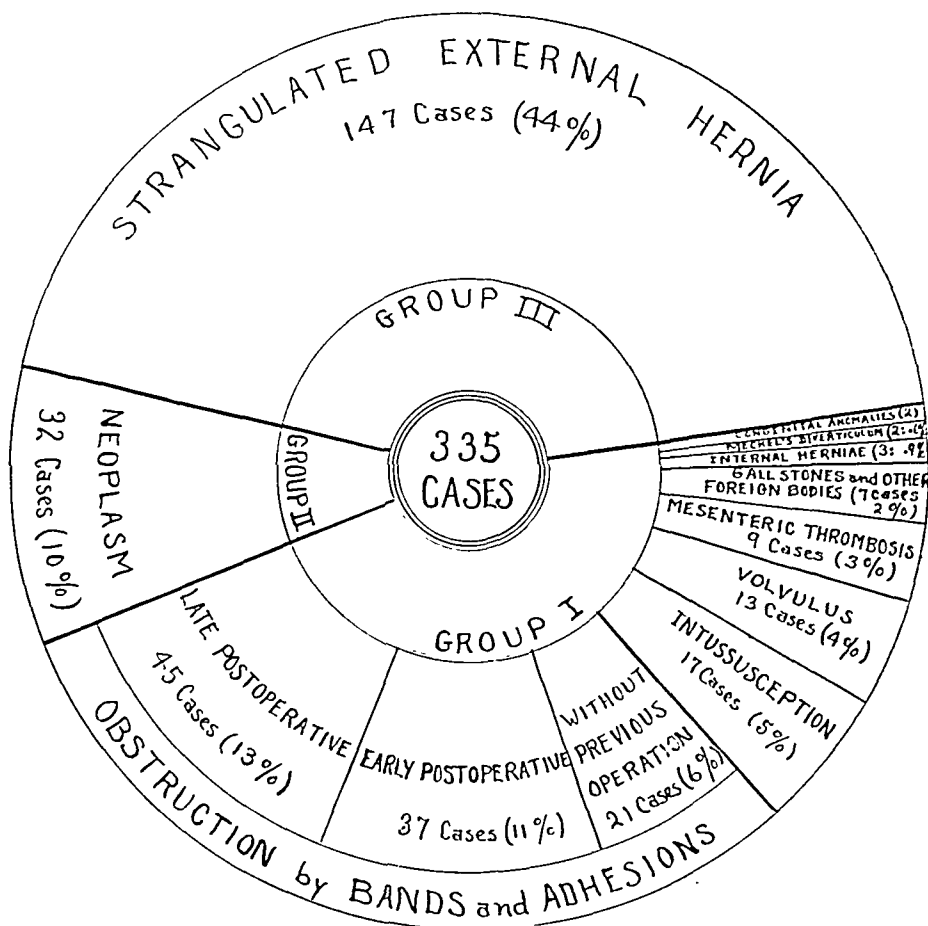


Chart 1.—Relative frequency of different types of obstruction.

for congenital anomalies and intussusceptions this was the only cause of obstruction in the first year of life.

*Changes in the Circulation of the Bowel.*—The fourth point of special interest is the changes that may take place in the circulation of the bowel. These come about in two ways. First, there may be gross interference with the mesenteric circulation; second, the capillary circulation in the wall of the bowel itself may be damaged by the increased intra-intestinal pressure of extreme distention. The relation between interference with the circulation and mortality will be presented in the later papers.

*Interference with the Mesenteric Circulation.*—It is now generally recognized that in a consideration of intestinal obstruction the mesentery must be regarded as an integral part of the intestine. This grouping

together of the mesentery and the intestine is of great importance, for most of the twists, knots, invaginations and strangulated loops that obstruct the intestinal lumen also in varying degrees snarl or compress the mesentery. When this interference is extreme, gangrene of the intestine follows, and the course of the disease is fulminating; the

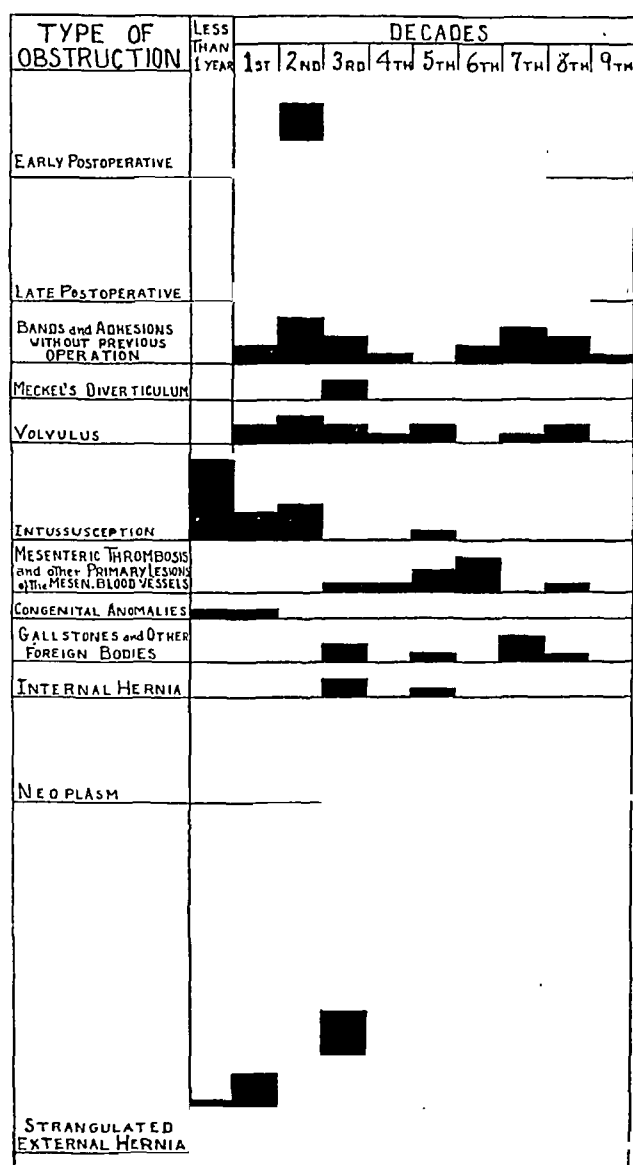


Chart 2.—Ages of patients with different types of obstruction.

pathologic and altered physiologic conditions are quite different from those in cases in which there is merely blockage of the intestinal lumen.

From table 3 it will be noted that 63 per cent of the total cases show some degree of interference with the mesenteric circulation (strangulation), the changes in the bowel varying from cyanosis and congestion to actual infarction. The figures for group I are presented in detail in the second paper in this series. In group II (obstructions

by neoplasms) only one case showed interference with the mesenteric circulation; this is due, of course, to the fact that in the great majority of these cases the obstruction comes about through blockage of the lumen by a growth originating within the bowel wall. All of the cases due to strangulated hernia, group III, showed some degree of interference with the mesenteric circulation. The problem in these cases must be considered as somewhat different, for the loop of intestine, with its involved mesentery, is for practical purposes outside the abdominal cavity and, from the point of view of early diagnosis, ease of management, and absorption from the involved loop, these cases present distinctive features which are discussed in detail in the paper on strangulated hernias.

*Interference with the Capillary Circulation.*—It is difficult to estimate from the operative notes the extent of the interference with the capillary circulation and the resulting damage to the bowel wall. This was

TABLE 3.—*Interference with Mesenteric Circulation in All Groups*

Classification	Number of Cases	Number Showing Mesenteric Interference	Per Cent Showing Interference
Group I (Acute mechanical obstructions, exclusive of those caused by neoplasms or by strangulated external hernias).....	156	66	42
Group II (Obstructions due to neoplasms)	32	1*	3
Group III (Obstructions due to strangulated external hernias).....	147	147	100
Total, All Causes.....	335	214	63

\* There were also two cases in which neoplasms caused mesenteric thrombosis; these are listed under that heading.

probably an important factor in a larger number of cases than is indicated by the following figures:

In group I there were nine instances in which it seemed, from the description of the bowel at operation, that there had been extensive damage from interference with the capillary circulation. In four of the nine recorded cases, bloody fluid was found on opening the peritoneal cavity. In group II, cases of obstruction from neoplasms, there were four instances in which there was obvious damage from distention—perforation or the beginning of necrosis of the cecum being found at operation. Great distention often accompanies obstruction of the colon by a neoplasm. This is particularly true in obstruction of the sigmoid when partial obstruction has existed for some time before becoming complete; in these cases the cecum is particularly likely to suffer from the effects of distention, areas of necrosis and perforation occurring on the anterior surface where the circulation is most vulnerable.

*Level of the Obstruction.*—A fifth point of interest is the distribution of the obstructions at different levels of the intestinal canal.



It is generally recognized that obstructions of the colon are less fulminating than those in the small intestine. Of course, however, if interference with the mesenteric circulation is present, death will occur as quickly in one situation as in another, as a result of the infarction of the intestine. It is also true in a general way that obstructions high in the small intestine are more rapidly fatal than those situated lower. This statement is strikingly true in regard to experimental obstructions in the lower animals,<sup>5</sup> and this fact has often colored the statements in regard to human cases, in which the differences between obstructions high and low in the small intestine are not so striking.

Table 4 shows the distribution at different levels of the intestine.

Two hundred and forty-nine cases occurred in the small intestine; twenty-seven in the large and small intestines together, and fifty-two in

TABLE 4.—*Level of the Obstruction*

Part of Bowel Obstructed	Classification of Cases *			Total Cases	
	Group I	Group II	Group III		Per Cent
Jejunum .....	7	1	0	8	
Ileum .....	59	2	0	61	
Small intestine (not further described) .....	53	0	127	180	
	119	3	127	249	74
Ileocolic intussusception.....	14	0	0	14	
Large and small intestine.....	0	0	13	13	
	14	0	13	27	8
Large intestine.....	16	29	7	52	15
Not determined ...	7	0	0	7	2
Total .....	156	32	147	335	

\* Group I: All acute mechanical obstructions except those due to neoplasms or strangulated external hernias.

Group II: Obstructions due to neoplasms.

Group III: Obstructions due to strangulated external hernias.

the colon. Of the cases occurring in the colon, twenty-nine were caused by neoplasms.

It will be observed that obstruction high in the intestinal tract was relatively rare; in only eight of the entire number of cases was it found as high as the jejunum. This is of importance in relation to experimental work in dehydration, for it is in simple high obstructions that the brilliant results in the prolongation of the life of animals by the administration of adequate volumes of solution of sodium chloride have been obtained. Of the eight patients in this series with high obstruction, five had gross

5. It has been shown by numerous observers that untreated simple high obstruction in dogs has a rapid, fulminating course; the animals usually dying in two or three days, whereas if the obstruction is situated lower in the small intestine the animals may live for days or even weeks.

interference with the mesenteric circulation, so that there were only three cases of simple high obstruction. These figures bear out the statement of McIver and Gamble<sup>6</sup> concerning the infrequency of this type of obstruction. A certain degree of dehydration usually accompanies obstruction at any level, but in the low obstructions more commonly occurring in human beings the loss of digestive secretions in the vomitus and the consequent changes in the blood plasma are less extensive than in high obstructions, and the results obtained by replacement of the loss with physiologic solution of sodium chloride, while valuable and occasionally dramatic, are usually less outstanding. Furthermore, in human cases, when interference with the mesenteric circulation is present this is a more important factor in the outcome than is the dehydration.

#### SUMMARY

1. Three hundred and thirty-five patients with acute intestinal obstruction of mechanical origin were operated on at the Massachusetts General Hospital during the ten years from 1918 through 1927.

2. The mortality in the total number of cases from all causes was 31 per cent. A detailed analysis of the figures on mortality is presented in the second and third papers of this series.

3. About one half of the cases of obstruction were due to strangulated external hernias and one-tenth to neoplasms. In group II, obstructions by bands and adhesions form by far the largest group; obstructions from intussusception come next, and the remaining cases represent rarer groups.

4. The correlation between the age of the patients and the different types of obstruction is shown.

5. Interference with the mesenteric circulation forms a serious and frequent complication in cases of intestinal obstruction, being present in varying degrees in 63 per cent of the cases of this series. The toxemia is often proportional to the resulting damage to the bowel.

Interference with the capillary circulation from distention is also important, but its extent is often difficult to determine; it was definitely present in thirteen cases of this series.

6. Two hundred and forty-nine cases showed obstruction in the small intestine; fifty-two in the large intestine. The relative infrequency of simple high obstruction is pointed out, and the relation of this fact to the results of experimental work on dehydration is discussed.

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6. McIver, M. A., and Gamble, J. L.: Body Fluid Changes Due to Upper Intestinal Obstruction, *J. A. M. A.* **91**:1589 (Nov. 24) 1928.

included. There were five cases in which an interintestinal abscess was present, four cases in which ileostomy or colostomy was carried out under diagnostic error and seven cases, two occurring in infants and five in aged persons, in which exploration was made for intestinal obstruction but no organic obstruction was found; none of these cases was included in the series.

Each admission was counted as one case. If obstruction recurred during the patient's stay in the hospital, as happened in several instances, it was counted as one case, and the final result only was recorded. There were one hundred and fifty patients, four of whom were admitted twice and one three times for operation for intestinal obstruction, making six more cases.

TABLE 1.—Mortality in Different Types of Cases

Type of Case	1898-1907		1908-1917		1918-1927	
	Num-ber of	Mor-tality, per cent	Num-ber of	Mor-tality, per cent	Num-ber of	Mor-tality, per cent
Early postoperative (within 4 weeks after operation).....	18	13	72	29	7	24
Late postoperative (more than 4 weeks after operation).....	19	6	32	28	11	39
Bands and adhesions without previous operation.....	33	18	54	14	7	50
Meckel's diverticulum.....	9	7	78	4	2	50
Volvulus.....	9	9	100	16	4	25
Intussusception.....	27	14	52	20	12	60
Mesenteric thrombosis.....	1	1	100	5	4	80
Congenital anomaly.....	2	2	100	..	..	..
Gallstone or other foreign body..	1	1	100	1	1	100
Strangulated internal hernia.....	2	2	100	1	7	3
Total.....	121	73	60	118	41	156

COMPARISON OF MORTALITY FIGURES FOR THIRTY YEARS

In the analysis of the cases of intestinal obstruction, all deaths, whether or not the direct result of the obstruction, were included. The cases are grouped as in the preceding series, the most important feature of each being used as the basis for classification, since certain cases have characteristics allying them to more than one group. There were many borderline cases in which decision was difficult, and the final arrangement must be considered as somewhat arbitrary.

Table 1 shows the grouping of the cases and the mortality in the three ten-year series.

The total mortality in the present series is essentially the same as that reported for the years from 1908 to 1917. In contrasting the cases occurring from 1898 to 1907 with those from 1908 to 1917, it will be noted that the most striking reduction in mortality was obtained

# ACUTE INTESTINAL OBSTRUCTION

## II. ACUTE MECHANICAL OBSTRUCTIONS EXCLUSIVE OF THOSE DUE TO NEOPLASMS AND STRANGULATED EXTERNAL HERNIAS

MONROE A. McIVER, M.D.

COOPERSTOWN, N. Y.

### SELECTION OF MATERIAL

In 1908, Scudder<sup>1</sup> reported a series of one hundred and twenty-one cases of acute intestinal obstruction of mechanical origin in which operation was performed at the Massachusetts General Hospital during the years from 1898 to 1907, inclusive. Cases of chronic or partial obstruction, cases of obstruction by strangulated external hernias and cases of obstruction due to neoplasms (except neoplasms that were an inciting cause of intussusceptions or mesenteric thromboses) were excluded. In 1920, Richardson<sup>2</sup> reported a second series of one hundred and eighteen cases, in direct continuation of the first series, occurring from 1908 to 1917, inclusive. He made every effort to have the series as nearly as possible parallel to the first, and stated that Dr. Scudder examined with him all doubtful and borderline cases.

The present study embraces the same types of cases observed from 1918 to 1927, inclusive. Every effort has been made to have the series as nearly as possible comparable with those that preceded it. To this end, Dr. Richardson, in 1929, collaborated in the examination of doubtful and borderline cases, making helpful suggestions as to the arrangement of the material.

The cases reported in this series, as in the preceding ones, are those of mechanical obstruction, or at least those with a mechanical element. In going through the records for this series, ten cases were found in which, although enterostomy had been performed, it was obvious that peritonitis was the chief factor, the obstructive features depending on a paralytic condition secondary to the peritonitis; these cases were not

From the Surgical Services of the Massachusetts General Hospital.

1. Scudder, C. L.: The Principles Underlying the Treatment of Acute Intestinal Obstruction; a Study of 121 Cases of Acute Intestinal Obstruction from the Massachusetts General Hospital Clinic, Tr. New Hampshire State M. Soc., 1908, p. 234.

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Type of Case	1898-1907 C. L. Scudder			1908-1917 E. P. Richardson			1918-1927		
	Num- ber of Cases	Num- ber of Deaths	Mor- tality, per Cent	Num- ber of Cases	Num- ber of Deaths	Mor- tality, per Cent	Num- ber of Cases	Num- ber of Deaths	Mor- tality, per Cent
Early postoperative (within 4 weeks after operation).....	18	13	72	29	7	24	37	17	46
Late postoperative (more than 4 weeks after operation).....	19	6	32	28	11	39	45	13	29
Bands and adhesions without previous operation.....	33	18	54	14	7	50	21	9	43
Meckel's diverticulum.....	9	7	78	4	2	50	2	0	0
Volvulus.....	9	9	100	16	4	25	13	6	46
Intussusception.....	27	14	52	20	12	60	17	9	53
Mesenteric thrombosis.....	1	1	100	5	4	80	9	9	100
Congenital anomaly.....	2	2	100	..	..	...	2	2	100
Gallstone or other foreign body..	1	1	100	1	1	100	7	2	27
Strangulated internal hernia.....	2	2	100	1	1	100	3	1	33
Total.....	121	73	60	118	49	41	156	68	44

## COMPARISON OF MORTALITY FIGURES FOR THIRTY YEARS

In the analysis of the cases of intestinal obstruction, all deaths, whether or not the direct result of the obstruction, were included. The cases are grouped as in the preceding series, the most important feature of each being used as the basis for classification, since certain cases have characteristics allying them to more than one group. There were many borderline cases in which decision was difficult, and the final arrangement must be considered as somewhat arbitrary.

Table 1 shows the grouping of the cases and the mortality in the three ten-year series.

The total mortality in the present series is essentially the same as that reported for the years from 1908 to 1917. In contrasting the cases occurring from 1898 to 1907 with those from 1908 to 1917, it will be noted that the most striking reduction in mortality was obtained

in the early postoperative obstructions. It is disappointing that this reduction was not maintained in the present series, the figure rising from 24 to 46 per cent; the mortality is distinctly lower than in the first period, but is still far from satisfactory.

Late postoperative obstructions and the obstructions due to bands and adhesions without previous operation show essentially the same mortality throughout the three periods, although there is a slight improvement. The obstructions from Meckel's diverticulum, although the group is small, show a definite improvement through the three periods. The obstructions from volvulus show a rise in mortality over the second period but a decided improvement over the first. The figures for intussusception are rather strikingly similar for the three periods. The mesenteric thromboses and congenital anomalies show only a single recovery throughout the thirty years of study. Obstructions from gallstones and other foreign bodies show two deaths in seven cases in the present series; there was only one case of this type of obstruction in each of the other series. The obstructions from internal hernias form a small group; there were two recoveries and one death in the present series.

#### ANALYSIS OF TYPES OF OBSTRUCTION SHOWN IN TABLE I<sup>3</sup>

Since the various types of obstruction present such distinctive pathologic and clinical pictures, they will be analyzed individually.

*Early Postoperative Obstruction.*—Acute obstructions are defined as "early postoperative" when they occur within four weeks of an operation.<sup>4</sup> The obstruction occurred within the first week after operation in nineteen cases, or about one-half the total number, and within the second week in seven cases. The average length of time between the first operation and the onset of obstructive symptoms was about seven days.

In this series there were thirty-seven cases<sup>5</sup> occurring early after operation, with seventeen deaths, a mortality of 46 per cent. This contrasts with a mortality of 72 per cent in the first series and 24 per cent

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3. These types of obstruction make up Group I as defined in the first paper of this series (McIver, M. A.: Acute Intestinal Obstruction. I. General Considerations, Arch. Surg., this issue, p. 1098).

4. One case of obstruction occurring later than the four-week period is included, since the patient was still in the hospital after the original operation when the obstructive symptoms arose.

5. There were, in addition, three instances in which volvulus of the small intestine occurred early after operation; in none of these cases was the twist tight enough to cut off the mesenteric circulation. There was one case in which mesenteric thrombosis followed soon after splenectomy. These instances represent cases that might be classified under two headings; following the precedent in the other series they are listed under volvulus and mesenteric thrombosis, respectively.

in the second. The high mortality in this series is partly explained by the fact that there were nine cases in which the first operation was for carcinoma of the rectum or sigmoid, with seven deaths.

The original operation in these cases was as follows:

Appendectomy .....	13
(with drainage, 9)	
Operation for carcinoma of the rectum.....	7
Operation for carcinoma of the sigmoid.....	2
Hysterectomy .....	3
Drainage of tubo-ovarian abscess.....	1
Closure of perforated gastric ulcer.....	1
Repair of ventral hernia.....	1
Miscellaneous .....	0

The obstruction is recorded as being in the following locations:

Lower ileum .....	16
Mid-ileum .....	3
Mid-jejunum .....	2
Small intestine, not further specified.....	9
Not recorded .....	7

The signs and symptoms were the usual ones of abdominal pain, vomiting, abdominal distention and failure to pass either gas or feces by rectum. The vomitus was described as "fecal" in six instances.

In the group of early postoperative obstructions the diagnosis often presents unusual difficulties. In the first place, the picture is frequently complicated by varying degrees of peritonitis (in twelve of the thirty-seven cases of the present series this played a definite rôle). In the second place, the onset of the obstructive symptoms is often insidious, the picture changing almost imperceptibly from that of a stormy convalescence with a considerable amount of vomiting and pain, which, however, might be expected to quiet down under conservative treatment, to one in which frank obstruction, demanding operative intervention, is recognized.

Visible peristalsis was recorded in seven cases. When present, it is a particularly helpful finding in this group in which diagnosis is often difficult.

In the consideration of treatment, it must be borne in mind that the pathologic process in these cases has certain distinctive features: The obstruction is usually due to recent inflammatory adhesions and is often complicated by local paralysis of the bowel from peritonitis. If drainage is instituted above the point of obstruction, the tension will be relieved, the bowel will regain its tone, and the inflammatory, fibrinous adhesions will often be absorbed without further operative procedures; thus these cases differ from other groups of obstructions caused by firmly organized, cicatricial bands and adhesions, which usually demand a direct attack before permanent relief can be obtained.



Enterostomy can of course be carried out under local anesthesia, without a thorough exploratory operation, which is of great advantage when the patient is very sick. The danger of overlooking a strangulated loop is not great; there was only one case in the present series of early postoperative obstructions in which strangulation was present, and in the series reported by Richardson there was likewise only one case that gave evidence of strangulation—a total of two cases in sixty-six. When it does occur, a rising white blood cell count may be useful in indicating its existence and suggesting the need of prompt operation.

Although strangulation is a rare complication in cases of obstruction early after operation, there were three instances in which volvulus occurred. In one case jejunostomy was performed without exploration; the symptoms were not relieved, and a later exploratory operation revealed the twist; the patient died. In the other two cases postoperative volvuli were discovered and relieved at exploration, the patients recovering.

It is obvious that the exact type of operation and the amount of exploration that should be done must be determined by the surgeon's judgment in each case. For the very sick patient, particularly if peritonitis is present, the simpler operation will often prove a life-saving procedure. Widespread separation of recent inflammatory adhesions may result in a tear of a friable, inflamed bowel; also the danger of spreading the existing peritoneal infection is grave. In this series, damage to the bowel from separation of adhesions occurred in four instances.

The following operations were carried out:

Enterostomy alone .....	17 cases 9 deaths
Enterostomy with lysis of adhesions.....	10 cases 5 deaths
Lysis of adhesions alone .....	9 cases 3 deaths
Entero-enterostomy with lysis of adhesions....	1 case 0 death

The fact that in the present series there were nine deaths in seventeen cases following enterostomy alone reflects the seriousness of the situation that was found, and does not mean that there was an error in the choice of operation.

The group of obstructions developing early after operation is interesting and important. The patients are under the care of the surgeon at the time of the onset of obstructive symptoms, so that there can be no shifting of the responsibility as to the choice of the optimum time for operation. It is a group of serious cases, and in many instances the sepsis for which the original operation was performed plays as large a rôle as the actual obstruction.

*Late Postoperative Obstructions.*—Among the obstructions occurring late after operation there were forty-five cases with thirteen deaths,

a mortality of 29 per cent. There is an improvement over the preceding series, the figures in those series being 32 and 39 per cent.

In sixteen instances the obstruction occurred within the first year after operation; the longest period before the appearance of obstructive symptoms was twenty-five years, and the average time, excluding the cases that occurred within the first year, was six years.

The original operation was as follows:

Appendectomy <sup>6</sup> .....	27
Repair of hernia (strangulated in 3 cases) .....	4
Pelvic operations on uterus or adnexa .....	8
Miscellaneous .....	6
	<hr/>
	45

In seven instances the patient had undergone more than one operation before the obstruction occurred.

The obstruction occurred in the small bowel in forty-three of the cases, as follows: jejunum, two cases; ileum, nineteen and "small intestine" (not further described), twenty-two. Two occurred in the large intestine.

Strangulation was present in twenty instances, with six deaths. The number of these strangulations, occurring in connection with old, thoroughly organized adhesions, is in strong contrast with the infrequency of strangulation in the early postoperative group, in which adhesions were recent and often fibrinous. Among the late postoperative cases in which strangulation was present, a gangrenous intestine was found in seven instances <sup>7</sup>; resection was performed, and there were four deaths.

*Bands and Adhesions Without Previous Operation.*—In this group there were twenty-one cases, with nine deaths, a mortality of 43 per cent. The mortality in this group is higher, in all three series, than it is in the group of late postoperative obstructions (table 4 of the first paper in this series <sup>3</sup>). The suggestion was made in Richardson's report on the preceding series <sup>2</sup> that the abdominal scar made the diagnosis of obstruction easier, and that therefore the patients with postoperative obstruction came to operation earlier than those who had not been previously operated on. In the present series, however, the time element did not seem to be a factor in explaining the difference in

6. Many of these operations took place in other hospitals, and it is therefore impossible to estimate the number of cases requiring drainage; the figures available indicate that the number was high.

7. Two of these seven cases are listed under volvuli. There were two other cases (listed under volvuli) in which volvuli were present but the intestine was not gangrenous; the patients recovered.

mortality, for the patients without previous operation were, on the average, explored for obstruction earlier than the group with post-operative obstruction.

The following finding is also of interest: The cases of late post-operative obstructions in which operation was performed in less than forty-two hours after the onset of symptoms showed a mortality of 0 per cent, whereas cases of obstructions caused by bands and adhesions without previous operation, in which operation was performed within the same time limit, showed a mortality of 37 per cent. It seems that the higher mortality must be explained on the basis of the other characteristics of the two groups rather than on the basis of the time that they came to operation. It should be noted in this connection that many of the obstructions by bands and adhesions without previous operation, occurred in older persons, a fact that is partly responsible for the high mortality: there were eight patients over 60 years of age, and five of the nine deaths occurred in this group. The question of age alone, however, probably does not explain the difference in mortality in these two groups.

The bands and adhesions causing these obstructions were usually of inflammatory origin. Tuberculous peritonitis was present in one case; mesenteric lymph glands enlarged or partly broken down furnished a chronic inflammatory focus in five. The obstruction was described as being due to adhesions in thirteen instances, and to bands in eight. In three of these cases the omentum acted as a band. There was interference with the mesenteric circulation in eight instances, but in only three of these was it of sufficient severity to demand resection of the intestine.

The large intestine was obstructed in five cases, and the small intestine in sixteen.

It is interesting to note in considering together the two groups of obstructions caused by bands and adhesions, without previous operation or late after operation, that in the cases in which the obstruction was described as being caused by a band, the mortality was only 22 per cent, whereas in those in which it was described as being caused by adhesions, the mortality was 55 per cent. The term "adhesions" was probably used to denote a more widespread pathologic condition; also, a definite band is more easily dealt with at operation.

*Meckel's Diverticulum.*—Meckel's diverticulum is among the rarer causes of acute intestinal obstruction. In producing obstruction it not infrequently acts as a band; it deserves separate consideration, however, because of the tendency of the diverticulum to necrose and perforate.

In this series there were two cases of Meckel's diverticulum, in both of which the patients recovered. In both instances there was interference with the mesenteric circulation of the obstructed loop of the bowel as

well as circulatory changes in the diverticulum itself; perforation of the diverticulum is a frequent complication in this type of obstruction. There was also one case included under intussusception in which Meckel's diverticulum was responsible for the intussusception. Among the cases of strangulated external hernia there was one in which, in addition to the omentum, an inflamed diverticulum was contained within the hernial sac.

*Volvulus.*—There were thirteen cases of volvulus, the acute obstruction being produced by torsion of the intestine and its mesentery. Among these cases there were six deaths, a mortality of 43 per cent. The mortality in this type of case shows a definite increase over the second series, but marked improvement over the first. The small intestine was involved seven times, and the large intestine six times (the cecum, three times and the sigmoid three). Seven patients in the group had been operated on previously, in four instances the volvulus occurring early after operation; in one of these cases the volvulus followed reduction of a strangulated hernia. In nine of the total of thirteen cases there was interference with the mesenteric circulation, producing changes in the bowel wall. This required resection in five cases, in which there were four deaths.

*Intussusception.*—There were seventeen cases of intussusception, with nine deaths, a mortality of about 53 per cent. A high mortality in this group was noted in all three series (table 1). This is a type of obstruction in which early diagnosis and operation are of the greatest importance. Among the nine who died there were only two patients who were received at the hospital within less than forty-eight hours after the onset of symptoms. This seems definitely to be a group in which the general practitioner can contribute greatly to the lowering of mortality by sending the patients to the surgeon earlier. The signs and symptoms, especially in infants, are usually distinctive.

Eleven of the cases of intussusception occurred in infants, with eight deaths. All these infants showed bleeding from the rectum; in eight instances an abdominal mass could be palpated. This contrasted with the older patients, in whom bleeding from the rectum was absent, and in only one of whom a definite mass could be palpated.

In thirteen instances the intussusception was of the ileocecal variety; in one instance the cecum was invaginated into the ascending colon. In three instances the intussusception was enteric, the small intestine alone being involved. As is usual in enteric intussusception,<sup>8</sup> these cases occurred in adults or young persons rather than in infants. In two

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8. McIver, M. A.: Intussusception of the Small Intestine with Special Reference to Meckel's Diverticulum as a Causative Factor, *New England J. Med.* **199**: 453 (Sept. 6) 1928.

instances, as is also common in enteric intussusception, there was a definite mechanical cause, Meckel's diverticulum in one, a polyp in the other.

The operations enumerated in the following tabulation were performed.

Operative Procedure	Number of Cases	Number of Deaths
Intussusception reduced .....	10	5
Resection with primary anastomosis .....	1	1
Resection with delayed anastomosis .....	1	0
Intussusception brought outside the wound and an enterostomy done .....	3	1
Miscellaneous <sup>9</sup> .....	2	2

*Mesenteric Thrombosis and Other Vascular Lesions.*—There were nine cases in which infarction of the intestine resulted from thrombosis of the mesenteric or portal system, or occlusion of one of the mesenteric arteries or their branches. All these patients died. On analysis it was obvious that most of them represented a hopeless situation from the outset. In three instances, metastatic neoplasm played a rôle by occluding an important branch of the mesenteric artery or vein. In three instances the whole portal system was involved in the thrombosis, with a resulting infarction of the entire small intestine. In one instance the infarction was due to arteriosclerotic occlusion of small branches of the superior mesenteric artery. There was one case (discussed with those of volvulus) in which mesenteric thrombosis followed the reduction of a volvulus that included the whole small intestine; the thrombosis was discovered at autopsy.

All the cases of mesenteric thrombosis involved the small intestine except one, in which there was an infarction of the sigmoid. There were only five instances in which resection was carried out.

It is well known that mesenteric thrombosis is characterized by extremely marked leukocytosis. It is interesting, however, from a diagnostic point of view that while this was true in the preceding series, it is not outstanding in the present one: There were only three patients in which the leukocyte count was above 20,000, the highest being 27,000; in the remaining patients the count was about 15,000.

*Congenital Anomaly.*—There were two cases occurring in infants in which congenital malformation was responsible for the obstruction. Both patients died.

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9. In one of these patients it was impossible to reduce or deliver the intussusception, and an enterostomy was done. In the other patient, who was moribund at the time of operation, the intussusception was not found at a hurried exploration; it was discovered at autopsy.

*Obstruction from a Gallstone or Other Foreign Body.*—There were seven cases (two deaths) in which the lumen of the intestine was obstructed by a foreign body.

In five instances, a gallstone was the etiologic factor; the deaths occurred among these cases. In three cases the gallstone was found impacted in the terminal ileum; in one it was in the ileocecal valve. In all these patients an enterostomy was done in addition to removal of the gallstone.

In one case the impacted material was green corn, which blocked the terminal ileum. In another there was an impaction of bran in the same location, the patient having eaten an enormous bowlful of this cereal the preceding day. In one instance it was possible at operation to milk the impacted material into the lumen; in the other it was necessary to perform an ileostomy.

One case which was included under those of late postoperative obstructions should be mentioned here, in which bismuth, administered by mouth for the purpose of a gastro-intestinal series, converted a subacute into an acute obstruction. Operation was without avail, the patient dying shortly after it had been performed.

*Strangulated Internal Hernia.*—There were three cases of strangulated internal hernia. In two instances there was a herniation through a hole in the mesentery; in one the herniation occurred through an opening in the omentum. Resection was carried out in two of the cases, continuity of the intestinal tract being reestablished at the time of operation in one, while in the other the ends of the intestine were brought out through the wound and the anastomosis was delayed until the patient's general condition should improve.

There was one death from pneumonia on the fifteenth day after operation.

#### GENERAL CONSIDERATIONS AFFECTING THE MORTALITY

There are certain factors that may affect the mortality: first, the length of time elapsing between the onset of the acute obstruction and its relief by operation; second, interference with the circulation of the bowel; third, the level of the obstruction, and fourth, the age of the patient.

*The Time Element.*—The time elapsing before operation is perhaps the most important factor, for, if sufficient time has elapsed for marked damage to the bowel to have occurred and for systemic effects to have manifested themselves, surgical measures are often unable to prevent a fatal termination, even though the obstruction is relieved. The relation of the time element to mortality is shown (for this series) in table 2. In one hundred and forty-nine cases the records were such that it was

possible to estimate approximately the duration of symptoms before operation. About half of the patients (seventy-three) were operated on within the first forty-eight hours, with a mortality of 26 per cent. The remainder, operated on beyond that period, showed a mortality of 60 per cent.

*Interference with the Circulation to the Bowel.*—Mesenteric Circulation: The amount of interference with the mesenteric circulation is a factor of greatest importance in the determination both of the acuteness of the illness and of the ultimate outcome: The greater the damage to the bowel, the more marked the toxemia. This has been known for

TABLE 2.—Duration of Symptoms

Duration of Symptoms	Number of Cases	Number of Deaths	Mortality, per Cent
Less than 24 hours.....	36	6	17
24 to 48 hours.....	37	13	35
Over 48 hours.....	76	46	60

TABLE 3.—Interference with the Mesenteric Circulation

Classification	Number of Cases	Number Showing Interference With Circulation	Mortality in Cases With Interference, per Cent	Mortality, Cases Without Interference, per Cent
Postoperative, early.....	37	2 (5%)	100	43
Postoperative, late.....	45	17 (38%)	29	28
Bands and adhesions without previous operation.....	21	8 (38%)	50	38
Meckel's diverticulum.....	2	2 (100%)	0	0
Volvulus.....	13	9 (69%)	55	25
Intussusception.....	17	17 (100%)	53	0
Mesenteric thrombosis.....	9	9 (100%)	100	0
Congenital anomaly.....	2	0	0	100
Gallstones and other foreign bodies.....	7	0	0	29
Strangulated internal hernias.....	3	2 (67%)	50	0
Total.....	156	66 (42%)	53	37

a long time, both from clinical observation and from experimental work (Bryant<sup>10</sup>; Murphy and Vincent<sup>11</sup>). Analysis of the present series brings out the validity of this point of view.

Table 3 shows that sixty-six patients (or 42 per cent of the total number) of the present series had some degree of interference with the mesenteric circulation, although in many cases this was not extreme. It will be noted that the mortality in patients showing interference with the mesenteric circulation was 53 per cent, as contrasted with 37 per cent in patients not having this complication. In table 4 (thirty year

10. Bryant, Thomas: Harveian Lectures, London, J. & A. Churchill, 1885.

11. Murphy, F. T., and Vincent, B.: An Experimental Study of the Cause of Death in Acute Intestinal Obstruction, Boston M. & S. J. 165:684 (Nov. 2) 1911.

period) it will be noted that about half the patients had interference with the mesenteric circulation and that the mortality among them was 62 per cent as contrasted with mortality of 41 per cent in those in whom the mesenteric blood supply was undisturbed. It is probable that these figures would be more striking but for the fact that when any element of strangulation is present the onset of symptoms is likely to be more fulminating and the pain often so extreme that the patient is brought early to operation. The favorable time element thus to some extent offsets the more serious pathologic condition.

TABLE 4.—*Interference with the Mesenteric Circulation During Thirty Year Period*

Period	Number of Cases	Number Showing Interference With Circulation	Mortality in Cases with Interference, per Cent	Mortality, Cases Without Interference, per Cent
1898 to 1907.....	121	59 (49%)	78	57
1908 to 1917.....	118	54 (45%)	55	30
1918 to 1927.....	156	66 (42%)	53	37
Total.....	395	179 (45%)	62	41

TABLE 5.—*Level of the Obstruction*

Part of Bowel Obstructed	1908-1917: E. P. Richardson			1918-1927		
	Number of Cases	Number of Deaths	Mortality, per Cent	Number of Cases	Number of Deaths	Mortality, per Cent
Jejunum.....	8	3	37	7	5	71
Ileum.....	28	8	28	59	24	41
Small intestine (not further specified).....	41	15	36	53	21	40
Ileocolic (intussusception).....	15	10	67	14	8	57
Large intestine.....	11	3	27	16	6	37
Not determined.....	15	10	67	7	4	57
Total.....	118	49		156	68	

Capillary Circulation: It is difficult to estimate statistically the relation of interference with the capillary circulation to mortality. Probably all cases in which the obstruction has existed for any appreciable length of time show some interference with the capillary circulation and resulting changes in the bowel wall, for it has been repeatedly shown that toxins are not absorbed through a normal intestinal mucosa. The amount of damage, however, is difficult to estimate.<sup>3</sup>

*Level of the Obstruction.*—The obstructions are listed in table 5 in the same manner as in the preceding series, on the basis of the part of the bowel involved, but no striking deductions can be made from the location of the obstruction in relation to the mortality. It is true that the seven cases occurring in the jejunum showed a high mortality in this series, but in a number of these patients there was such a serious interference with the mesenteric circulation that infarction of the intes-



tine resulted. This, of course, was a much more important factor than the level of the obstruction. A further discussion of the significance of the level of the obstruction was given in the first paper of this series.<sup>3</sup>

*Influence of Age.*—It will be noted from table 6 that the age of the patients has a definite relation to the death rate, the mortality being very high in those under 1 year of age, and also, in this series, in patients over 50.

#### DIAGNOSIS AND TREATMENT

*Diagnosis.*—The importance of the time element has been pointed out. The value of early diagnosis in acute intestinal obstruction has been recognized for the past thirty years, and yet cases repeatedly come to operation too late for the intervention to be successful. This must mean that diagnosis is often difficult. It is particularly so in cases in which a subacute obstruction becomes acute. Acute strangulations, how-

TABLE 6.—*Age in Relation to Mortality*

Age of Patient	Number of Cases	Number of Deaths	Mortality, per Cent
Under 1 year.....	10	6	60
1-10 years.....	11	5	45
10-20 years.....	28	8	29
20-30 years.....	27	8	30
30-40 years.....	24	6	25
40-50 years.....	20	11	55
50-60 years.....	13	8	61
60-70 years.....	13	8	61
70-80 years.....	9	7	78
80-90 years.....	1	1	100
Total.....	156	68	44

ever, usually do not present such difficulties in diagnosis, for, although it may not be possible to define the exact pathologic condition present, it is usually evident from the severity of the picture that an exploratory operation is demanded. Intussusceptions also, particularly those occurring in infants, are usually easy to diagnose, and it is distressing that the patients with intussusception in this series were brought to the hospital so late.

As pointed out by Miller,<sup>12</sup> the general practitioner is not always the one who fails to make a prompt diagnosis. Delays at times occur when the patient is under the care of the surgeon from the onset of the obstruction, and the situation is often temporized with until the optimum time for operation has passed. This is particularly likely to be the case in obstructions occurring early after operation, in which the picture is complicated. It must always be remembered that the condition of the patient is often more serious than it appears to be, and that a change

12. Miller, C. J.: Study of 343 Surgical Cases of Intestinal Obstruction, *Ann. Surg.* 89:91 (Jan.) 1929.

for the worse may take place with great rapidity. These patients are often far poorer operative risks than their general condition suggests. "If we wait until the patient's general condition shows the effect of the obstruction, the favorable time for operation is past" (Richardson<sup>2</sup>).

*Signs and Symptoms.*—The cardinal symptoms of obstruction are pain, vomiting and obstipation. Pain was present as a symptom in all of the patients of the present series; it varied greatly in intensity and location. With strangulations it is often agonizing from the beginning. In obstructions of the small intestine, the pain is colicky at first and likely to be localized in the region of the umbilicus; after from twelve to twenty-four hours, the pain is constant. When the obstruction is in the large intestine and has existed for some time, the pain and tenderness are often localized over the site of the obstruction, probably because of edema and infection.

Vomiting is also a constant symptom, the vomitus in the later stages of the disease consisting of the yellowish, foul-smelling fluid so characteristic of the contents of the obstructed small intestine. Obstipation may not be complete; at the onset, fecal material coming from the intestine below the point of obstruction may be passed or may be obtained by enema. Failure to obtain even gas on the administration of subsequent enemas is an important point, and in conjunction with abdominal pain should suggest to the attending physician the necessity of at least placing the patient under the observation of a surgeon.

Physical signs are often not characteristic. The temperature and the pulse and respiratory rates are not likely to be elevated early in the disease. The leukocyte count may be normal; a high white count, however, is suggestive of interference with the circulation and the need of early operation. Abdominal tenderness on palpation was recorded in sixty-one instances and muscle spasm in thirty-seven. In cases of strangulation, there is likely to be tenderness over the site of the strangulation; when the obstruction has existed for some time, the tenderness may be located just above the point of obstruction. Distention is usually present, but may be absent early and may not be marked even later in the disease if the obstruction is high in the intestinal tract. Visible peristalsis was noted in only twenty-two of the one hundred and fifty-six cases; it occurred with greatest frequency in the cases of early and late postoperative obstructions. A palpable mass due to a distended coil was recorded in only eight instances.

*Operations.*—Anesthesia: Table 7 shows the relation of the type of anesthesia employed to the mortality during the past twenty years. It is interesting that cases in which local anesthesia was used show such a high mortality as compared with those in which ether was employed.

This observation is also shown in a table by Miller.<sup>12</sup> It must certainly be accounted for on the basis of the fact that the operations in the more desperate cases were done under local anesthesia. It is well known that if the case is advanced, the use of ether is very dangerous; it may contribute to the shock after operation and may interfere with the return of peristalsis to the intestine after the mechanical obstruction has been relieved. The postoperative pulmonary complications are frequent, and the danger that the patient may vomit and aspirate intestinal contents during the course of the anesthesia is often a very real one, which is not entirely obviated by washing out the stomach before operation.

Ethylene is in many respects an ideal anesthetic for use in cases of intestinal obstruction. The dangers from explosion are such, however,

TABLE 7.—*Types of Anesthesia*

Type of Anesthesia	1908-1917: E. P. Richardson			1918-1927		
	Number of Cases	Number of Deaths	Mortality, per Cent	Number of Cases	Number of Deaths	Mortality, per Cent
Ether.....	99	41	41	99	35	35
Spinal anesthesia.....	7	1	14	1*	0	0
Spinal and general anesthesia.....	2	1	..	0	0	0
Local anesthesia (procaine hydrochloride).....	4	2	..	29	20	69
Procaine hydrochloride and general anesthesia.....	4	4	..	10	6	60
Gas-oxygen.....	2	0	..	8	6	75
Ethylene.....	0	0	0	9†	1	11
Total.....	118			156		

\* Spinal anesthesia has been used much more frequently since 1927 in operating on these patients.

† The use of ethylene has been abandoned at this clinic because of the explosion hazard.

that its use has been abandoned in the clinic of the Massachusetts General Hospital.

Type of Operation: The types of operation were of course numerous. As in the preceding reports, they have been grouped somewhat arbitrarily under the following heads: (1) relief of the obstruction only (this would include separation of bands and adhesions, reduction of intussusceptions, untwisting of volvuli, etc.); (2) relief of obstruction and drainage; (3) drainage only; (4) resection with immediate or delayed anastomosis, and (5) miscellaneous procedures that could not be grouped under the foregoing headings. The results are shown in table 8.

It will be noted that in those cases in which relief from the obstruction alone was attempted the mortality was by far the lowest. These cases were, in general, those that came to operation early in the disease.

When drainage of the bowel was carried out, either alone or in combination with relief from the obstruction, enterostomy was done in fifty instances, and colostomy or cecostomy in ten. Of the fifty enterostomies, eight were described as jejunostomies; there were four deaths. In the majority of the remaining enterostomies it was difficult to tell at what level the operation had been performed but frequently it was either in the presenting loop of distended intestine or just above the point of obstruction. If the obstruction is not first relieved, jejunostomy may be a dangerous operation.<sup>13</sup>

The mortality in the cases in which drainage was used was high, about 56 per cent (table 8). Among the patients who recovered, however, there were unquestionably some who would have died if more radical procedures had been attempted; but when extensive damage and

TABLE 8.—*Types of Operations*

Type of Operation	Number of Cases	Number of Deaths	Mortality, per Cent
Relief of obstruction only.....	68	13	19
Relief of obstruction and drainage.....	27	15	55
Drainage only.....	33	19	58
Resection { Immediate anastomosis.....	9	7	73
{ Delayed anastomosis.....	13	9	
Miscellaneous*.....	6	5	83
Total.....	156	68	44

\* There were two cases in which because of the condition of the patient the operation was abandoned, and one case in which due to diagnostic error the obstruction was not relieved.

absorption of toxin have already occurred, drainage may be powerless to save the patient.

In the group of resections, the mortality was high. Once the bowel has become gangrenous there is only a short period within which operation can save the patient; if many hours elapse before operation, so much toxic absorption takes place that removal of the damaged intestine is without avail. There were twenty-two resections in this series, with sixteen deaths, a mortality of 73 per cent. In nine of these patients the anastomosis reestablishing the continuity of the intestinal tract was carried out immediately; there were seven deaths. In thirteen cases the gangrenous intestine was resected, the ends of the intestine brought out and anastomosis reserved for future operation; there were nine deaths. Enterostomy was combined with resection in four cases.

13. Dr. D. F. Jones said: "I doubt the value of a jejunostomy in most cases, for if the obstruction is low the peristalsis below the jejunostomy will prevent the obstruction from letting up. This is particularly true in postoperative obstruction."

The number of cases is too small to throw any light on the relative safety of immediate as against delayed anastomosis. In the very sick patient the safest procedure is usually merely to remove the gangrenous intestine and to bring the ends outside the abdominal wound. One must be governed by the condition of the patient, the level of the obstruction and the type of anesthetic used. Infants, of course, tolerate intestinal fistulas poorly.

*Character of the Peritoneal Fluid Found at Operation.*—Blood-stained serum is likely to be found in the peritoneal cavity at operation in cases in which interference with the circulation of the bowel exists. Its presence is a helpful and significant finding to the surgeon, indicating as it does that a strangulated intestine must be sought. There were twenty-one instances in which blood-stained fluid was present and a gross interference with the mesenteric blood supply found. In a number of instances the fluid was described as foul-smelling, indicating extreme damage to the bowel. There were four cases in which bloody fluid was present but no definite interference with the mesenteric circulation found; the fluid in these cases was probably the result of the great distention and congestion of the obstructed intestine.

In twenty-seven cases in which there was interference with the mesenteric circulation, the presence or absence of bloody fluid was not mentioned in the operative notes. There were also a few cases in which, although there was interference with the mesenteric circulation, it was definitely stated that there was no bloody fluid. Its presence must depend on the degree and duration of interference with the mesenteric circulation; it represents an important operative finding, but its absence, particularly in cases brought early to operation, does not preclude the possibility of strangulation.

*The Treatment of Dehydration.*—In 1912, Hartwell and Hoguet<sup>14</sup> made the important discovery of the value of physiologic solution of sodium chloride in prolonging the lives of animals with simple high obstruction of the intestine. In 1923, Haden and Orr<sup>15</sup> reported the lowering of the blood chlorides in intestinal obstruction and confirmed the observations of Hartwell and Hoguet on the value of solution of sodium chloride in prolonging life.

Owing largely to the work of Haden and Orr and the general interest in the subject that their ideas created, treatment of the dehydration that usually accompanies intestinal obstruction by the administration

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14. Hartwell, J. A., and Hoguet, J. P.: Experimental Intestinal Obstruction in Dog with Special Reference to the Cause of Death and the Treatment by Large Amounts of Normal Saline Solution, *J. A. M. A.* **59**:82 (July 13) 1912.

15. Haden, R. L., and Orr, T. G.: Chemical Changes in Blood After Intestinal Obstruction, *J. Exper. Med.* **37**:365 (March) 1923.

of large volumes of physiologic solution of sodium chloride and dextrose, is now a generally accepted procedure.<sup>16</sup> Frequent measurements of the blood chlorides furnish important information as to the extent of the dehydration and depletion of the body tissues of the chloride ion.

During the last four years of the period embraced in this study, several physicians in the clinic were especially interested in this phase of the problem, and every effort was made to see that all patients with intestinal obstruction received adequate treatment with solution of sodium chloride. It was the general opinion that these measures were distinctly worth while, and in a number of instances were life-saving procedures. When, however, the present ten year series as a whole is contrasted with the series of from 1908 to 1917, no lowering of the total mortality is shown; also, when the mortality of the last four years of the present study is contrasted with that of the first six years, no reduction is found. This can probably be explained by the following facts: First, as pointed out by McIver and Gamble,<sup>17</sup> simple high obstruction in man, the only type comparable to the experimental obstructions in animals used in the work on dehydration,<sup>18</sup> is relatively rare; this is borne out by the figures in table 4 of the first paper in this series,<sup>3</sup> which showed that less than 10 per cent of the obstructions were situated in the upper jejunum. Second, when damage to the bowel exists, owing to interference with the circulation, the factor of dehydration is relatively unimportant, the disease having such a rapid course that the extreme degree of dehydration and loss of chloride ion do not have time to develop; in this group, 63 per cent of the cases showed some interference with the mesenteric circulation, and there were a number in which damage to the capillary circulation by distention undoubtedly played an important rôle.

Thus, in the great majority of cases with acute intestinal obstruction there are factors that outweigh dehydration in importance. Some degree of dehydration, however, is usually present in acute obstruction, and it is often extreme. Proper attention to this factor by the adminis-

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16. Early in their work Haden and Orr advanced the theory that the chloride ion neutralized some toxin absorbed from the obstructed intestine. They later abandoned this theory. The original idea, however, continues to crop up in the literature. I wish to emphasize the fact that salt solution merely compensates for the loss of body fluid; it does not neutralize any toxin absorbed from the damaged intestine.

17. McIver, M. A., and Gamble, J. L.: *Body Fluid Changes Due to Upper Intestinal Obstruction*, J. A. M. A. **91**:1589 (Nov. 24) 1928.

18. As shown by Hartwell and Hoguet and numerous other experimenters, when dogs with simple high obstruction of the jejunum are treated with sufficient quantities of salt solution to replace the volume of fluid lost in the vomitus, instead of dying within a few days they may live as long as three weeks although the obstruction is unrelieved.

tration of adequate volumes of salt solution before and after operation will improve the general condition of most patients, and in a certain number will be a decisive factor in the outcome.

#### SUMMARY

1. Data are presented on a third ten-year series (for 1918 to 1927, inclusive) of cases of acute intestinal obstruction of mechanical origin, excluding obstructions due to neoplasms or to strangulated external hernias. This report is comparable to previous studies by Scudder and Richardson for 1898 to 1917, inclusive.

2. The mortality in this series was 44 per cent, contrasting with 41 per cent in the years from 1908 to 1917 and 60 per cent in the period from 1898 to 1907 (table 1). A detailed analysis of the mortality in the different types of obstruction is presented.

3. There are three outstanding factors that affect the mortality: first, the lapse of time between the onset of the obstruction and the operation; second, the degree of interference with the circulation of the bowel; and third, the age of the patient.

4. Pain was recorded in all of the cases; vomiting was also a constant symptom, and distention was usually present. Visible peristalsis was recorded in only twenty-two instances, occurring chiefly in the early and the late postoperative obstructions. Abdominal tenderness was recorded in sixty-one instances (a little less than half), and muscle spasm in thirty-seven. Elevation of the white count is suggestive of strangulation and the need of immediate operation.

5. The types of anesthesia and operations are classified, and their relation to the mortality is discussed. A local anesthetic should be used in cases coming late to operation. The figures showed a low mortality for ether anesthesia as contrasted with local, but this was interpreted on the basis of the fact that operation in the more desperate cases was done under local anesthesia.

6. Treatment of dehydration by the administration of adequate volumes of physiologic solution of sodium chloride is extremely important. During the last four years of the present series, however, special attention was paid to this phase of treatment, and although it was felt to be a life-saving measure in certain cases, no lowering of the mortality rate as contrasted with that of other years was found. The explanation is offered that while dehydration is usually an important factor in obstructions at any level, it is most striking in simple high obstructions. Such cases are relatively infrequent, the obstructions are usually low and are often complicated by interference with the circulation of the bowel, a more important factor in determining the outcome than is dehydration.

## ACUTE INTESTINAL OBSTRUCTION

### III. OBSTRUCTION DUE TO NEOPLASMS AND STRANGULATED EXTERNAL HERNIAS

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#### A. OBSTRUCTION FROM NEOPLASMS, GROUP II

*Selection of Material.*—Part A of this paper includes data on all cases (thirty-two) of acute intestinal obstruction brought about by primary or metastatic neoplasms in which the patients were treated at the Massachusetts General Hospital in the years from 1918 to 1927, inclusive. Cases in which it was possible to temporize and to choose the optimum time for operation were considered subacute or incomplete and have been excluded.<sup>1</sup>

There were six cases of acute obstruction of the large intestine in which a tumor was presumably the cause. Owing to the serious condition of the patients at the time of operation, no exploration was carried out. These cases have been included.

One patient refused operation. Although the diagnosis was verified at autopsy, this case was not included.

*Mortality.*—The grouping of the cases on the basis of etiology and mortality is shown in table 1. Among the patients who recovered from acute obstruction, there were four who died during the same hospital admission, following a later resection of the neoplasm. These deaths have not been included, since there were no obstructive symptoms at the time of the second operation.

It will be noted that half of the deaths occurred in the cases listed as "presumably" being due to tumor. These patients were in such poor condition at the time of operation that a cecostomy or colostomy only was carried out, and consequently an exact diagnosis was never made. Only five deaths (or about 19 per cent) in cases of acute obstruction were proved to be due to neoplasms. It will be noted that the

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From the surgical services of the Massachusetts General Hospital.

1. The group of subacute cases is large in obstructions due to neoplasms. There were twenty-four cases in which the symptoms were of sufficient severity to warrant the term "subacute" or "partial" obstruction. The average duration of subacute symptoms was five and one-half weeks. If these patients had been sent to the hospital earlier, much valuable time could have been saved, not only from the point of view of removal of the obstruction, but as regards an earlier attack on the neoplasm.



obstructions in twenty-two of these cases were in the large intestine, while only four were in the small intestine; simple acute obstruction of the colon is a less fulminating disease than obstruction of the small intestine and, if operation is performed within a reasonable time after onset of symptoms, should show a low mortality.

*Etiology.*—The primary neoplasms causing obstruction of the large intestine were all adenocarcinomas arising from the mucosa of the bowel. For the most part these were annular tumors that gradually obliterated the lumen of the intestine. The tumor was often surprisingly small.

A primary neoplasm arising from the small intestine is, of course, rare. There were only two such in this series of cases, both carcinomatous.

The metastatic tumors originated from the uterus or ovaries in four cases, usually causing obstruction in the region of the sigmoid. In one

TABLE 1.—*Etiology and Mortality*

	Number of Cases	Number of Deaths	Mortality
Obstruction from primary tumor.....	20	4	
Large intestine .....	17		
Small intestine .....	3		
Obstruction from metastatic tumor.....	6	1	
Large intestine .....	5		
Small intestine .....	1		
Obstruction presumably due to tumor.....	6	5	
Large intestine .....	6		
Total.....	32	10	31%

case the primary focus was in the stomach; in the remaining cases the site of origin was not discovered.

*Interference with the Mesenteric Circulation.*—Interference with the mesenteric blood supply by strangulation is rare in cases of obstruction due to neoplasm. There were, however, three cases in which the neoplasm directly involved the mesenteric vessels, resulting in occlusion or thrombosis with consequent infarction of the intestine. These cases have already been discussed in the second paper of this series.<sup>2</sup>

*Age and Sex.*—In this series there were fourteen men and twelve women. The ages ranged from 28 to 90 years, the average being 55 years. Almost 60 per cent of the patients were over 60 years of age.

*Location of the Obstruction.*—The location of the growth in the proved cases of obstruction by neoplasm is shown in table 2. In all

2. McIver, M. A.: Acute Mechanical Obstruction: II. Acute Mechanical Obstructions Exclusive of Those Due to Neoplasms and Strangulated External Hernias, Arch. Surg., this issue, p. 1106.

but four instances the obstruction occurred in the large intestine, the sigmoid being the portion involved in 73 per cent of the total number.

It will be noted that there were no cases of acute obstruction from carcinoma of the rectum. This relatively common tumor of the intestinal tract often produces symptoms of subacute obstruction, but the blockage is rarely complete.

*Signs and Symptoms.*—The symptoms of acute obstruction from neoplasm are in general those that accompany acute obstruction from any cause in which strangulation is not present, namely, obstipation, pain, distention and vomiting. Since most of these obstructions are located in the large intestine, the symptoms have a tendency to be less fulminating than if the obstructions were located in the small bowel, and considerable time is likely to elapse between their onset and the time of operation. In this series of cases the average time between the

TABLE 2.—Location of Neoplasms

Portion of Bowel Obstructed	Number of Cases	Primary Neoplasm	Metastatic Neoplasm
Large intestine			
Sigmoid .....	16	11	5
Splenic flexure .....	3	3	0
Transverse colon .....	1	1	0
Hepatic flexure .....	2	2	0
	— 22	— 17	— 5
Small intestine			
Jejunum .....	1	1	0
Terminal ileum and cecum*.....	1	1	0
Lower ileum .....	2	1†	1
	— 4	— 3	— 1
Total.....	26	20	6

\* Described by Dr. J. H. Wright as "the so-called multiple carcinoma of the small intestine and appendix."

† A tumor involving the mesentery, the exact type not determined.

onset of acute symptoms and the operation was about five days. In some cases, the obstructive symptoms were very severe for from ten days to two weeks. The obstruction was probably not complete during that entire period, but it was impossible to say at what time the blockage became absolute. Since strangulation is rarely present in these obstructions, the pain may not be particularly severe. It is, however, almost constantly present and is likely to be described as cramplike or colicky. In the early stages it is usually localized across the lower part of the abdomen. In some instances acute discomfort from distention is the most outstanding complaint.

Vomiting occurs early with the onset of acute obstruction, but is not likely in the early stages to be so profuse or frequent as in obstructions of the small intestine; in the later stages, after the obstruction has become well established and the small intestine is more and more involved in the obstructive process, the vomiting may be profuse and of the typical "fecal" character.

Distention is likely to be marked in obstructions of the large intestine. In the early stages, visible peristalsis of the large intestine above the point of obstruction is not infrequently seen. When one attempts to say whether an obstruction is complete or not, the question of whether there is any passage of flatus, either voluntarily or on the administration of an enema, is an important criterion. The character of the vomitus should be carefully observed; if it takes on the character of small intestinal contents, prompt surgical intervention should be undertaken, even though some flatus is being passed by rectum.

There is usually little or no systemic reaction, the temperature and white blood cell count generally being normal.

*Duration of Symptoms.*—Sixteen of these patients (half the total number) had an unmistakable history of subacute obstruction antedating the acute obstruction by from ten days to several months, the average duration being not quite nine weeks. It is sad that a diagnosis was not made earlier, so that the acute obstruction could have been pre-

TABLE 3.—*Type of Anesthetic Employed*

Anesthetic	Number of Cases	Number of Deaths
General .....	13	3
Ether .....	12	
Gas oxygen .....	1	
Local .....	17	7
In a few cases supplemented by a general anesthetic		
Spinal .....	2	0

vented and much time saved in the removal of the cancer. The symptoms of subacute obstruction that antedated the acute attack were usually increasing constipation and episodes of cramplike pains in the lower part of the abdomen. At times frequent small movements may be the outstanding symptom. Dr. D. F. Jones has advanced the dictum that "any change of bowel habit in a patient in the cancer age demands an investigation to rule out the possibility of carcinoma of the large bowel or rectum." If this were carried out, there would be few cases of acute obstruction from neoplasm.

*Operation.*—Anesthesia: The anesthetic used is shown in table 3. Local or spinal anesthesia is, in general, most satisfactory for these patients, who are often aged and in poor condition for general anesthesia.

Type of Operation: Cecostomy or colostomy was carried out in twenty-five cases; enterocolostomy once. In the presence of obstructive symptoms no effort was made to resect any tumor of the large intestine.

In tumors involving the small intestine, resection was carried out in two instances. In one of these cases the involved segment of intestine was not considered viable, owing to interference with its blood supply.

## SUMMARY

1. From 1918 to 1927, inclusive, thirty-two patients with acute intestinal obstruction caused by neoplasm were treated at the Massachusetts General Hospital. There were ten deaths, a mortality of 31 per cent.

2. The group included obstructions caused both by metastatic and by primary tumors. The obstruction was located in the small intestine in four instances, and in the large intestine in twenty-eight.

3. The symptoms in general were obstipation, pain, distention and vomiting. The symptoms are usually less fulminating than in other types of acute obstruction. Sixteen of the patients gave a history of subacute obstruction antedating the acute attack by from ten days to several months.

4. Local or spinal anesthesia is, in general, the most satisfactory type.

5. Cecostomy or colostomy was the usual operation. In the presence of obstructive symptoms, no resection of the large intestine should be carried out as a primary operation.

B. ACUTE OBSTRUCTION DUE TO STRANGULATED EXTERNAL HERNIA,  
GROUP III

*Selection of Material.*—This report includes all cases of strangulated external hernia in which the patients were treated at the Massachusetts General Hospital in the ten year period from 1918 to 1927, inclusive. During the period covered there were one hundred and forty-seven cases of acute strangulated hernia, this important group causing almost one half of all cases of acute intestinal obstruction (chart 1 of the first paper of this series<sup>3</sup>). Some of the cases were discussed in Richardson's report<sup>4</sup> on strangulated hernias for the period from 1912 to 1921, but for the sake of completeness they have been included here also.

In the selection of the types of cases to be studied, cases of irreducible or incarcerated hernia in which there was no evidence of strangulation were excluded, and fourteen cases in which the omentum, but not the bowel, was strangulated in the hernial sac were excluded.

*Factors Affecting Mortality.*—As shown in table 4, there were twenty-seven deaths, a mortality of 18 per cent. By far the highest mortality was in the cases of umbilical and ventral hernias. These hernias are often found in fat, middle-aged persons, who are poor

3. McIver, M. A.: Acute Intestinal Obstruction: I. General Considerations, Arch. Surg., this issue, p. 1098.

4. Richardson, E. P.: Boston M. & S. J. **183**:288 (Sept. 2) 1920.

operative risks. There were proportionally more deaths among the patients with femoral hernia than among those with inguinal hernia.

*Duration of Symptoms Before Operation.*—As in all types of intestinal obstruction, delay in operation increases the mortality rate. In this series one-half the number of deaths occurred in patients in whom symptoms of strangulation had existed for more than twenty-four hours, as follows:

Symptoms of less than 24 hours' duration, 103 cases, 13 deaths, mortality 13 per cent.

Symptoms of more than 24 hours' duration, 44 cases, 13 deaths, mortality 30 per cent.

*Necrosis of the Bowel.*—Another important factor in the mortality rate is damage to the bowel through interference with the circulation. All cases of strangulated hernia show some interference with the mesenteric circulation. In nineteen cases of the present series, as shown in table 5, this was so severe and so persistent as to produce necrosis

TABLE 4.—*Factors Affecting Mortality*

Type of Case	Cases		Number of Deaths	Mortality, per Cent
	Number	Per Cent		
Inguinal.....	84	57	10	12
Femoral.....	34	23	6	18
Umbilical.....	18	12	8	44
Ventral.....	9	6	3	33
Epigastric.....	2	2	0	0
Total.....	147		27	18

of the bowel. Eleven deaths, almost half the total number, occurred within this small group of cases. When the damaged intestine lies within the sac of an external hernia, there is, perhaps, less rapid absorption of toxins than when it lies free within the abdominal cavity as in other forms of intestinal obstruction; but in spite of this fact, these cases showed a mortality of over 50 per cent.

*Complications.*—There was sudden death from pulmonary embolus in two cases; in another case a pulmonary embolus occurred but was not of sufficient size to cause death. There were four cases in which pneumonia followed the operation, in two instances the pneumonia being of the terminal hypostatic type. There was one death from purulent bronchitis and fatty degeneration of the liver. Uremia accounted for one death.

Eleven patients did not rally from the operation, and postoperative shock was put down as the cause of death. In eight of these cases, necrosis of the bowel was found at operation; presumably absorption of toxic material contributed to the "shock." In two of the patients autopsy showed general peritonitis.

There were four deaths among patients who still showed signs of intestinal obstruction (vomiting, great distention) after reduction of the hernia. Enterostomy was carried out as a secondary operation on all these patients but no improvement followed.

One patient died of a gas bacillus septicemia; at the time of operation there was an escape of a small amount of intestinal contents from the

TABLE 5.—*Cases Showing Necrosis of Bowel*

Type of Case	Portion of Bowel Obstructed	Duration of Symptoms	Type of Operation	Anesthetic	Result
Femoral 8 cases	Small intestine	5 days	Resection; ends brought out	Spinal procaine hydrochloride	R*
		7 days	Resection; ends brought out	Ether	R
		3-4 days	Resection; ends brought out	Procaine hydrochloride	D*
		30 hours	Resection; end to end anastomosis	Ether	D
		7 days	End to end anastomosis.....	Ether	D
		2 days	End to end anastomosis.....	Apothesine, spinal	R
		4 days	Inversion of necrotic area and enterostomy 8 inches above repair	Procaine hydrochloride	D
		8 days	Small necrotic area perforated; catheter placed in opening	Procaine hydrochloride	R
Inguinal 5 cases	Small intestine	16 hours	End to end anastomosis.....	Spinal procaine hydrochloride	R
		?	Resection; lateral anastomosis	Spinal apothesine supplemented by ether	D
	Small intestine	3 days	Inversion .....	Procaine hydrochloride	R
		1 day	Gangrenous loop brought outside of peritoneum but not outside of muscle	Procaine hydrochloride	R
	Transverse colon or sigmoid	4 days	Loop brought out; Mixer tube	Procaine hydrochloride	D
Umbilical 5 cases	Small intestine	4 hours	Resection; ends brought out	Ether	D
		24 hours	Resection; lateral anastomosis	Spinal procaine hydrochloride	D
		5 days	Loop of bowel brought out; Mixer tube	Ethylene	D
	Small intestine and transverse colon	4 days	Resection of small intestine; anastomosis	Ether	D
	Transverse colon	15 hours	Ends brought out.....	Ether	D
Epigastric 1 case	Small intestine	2 days	Resection; lateral anastomosis	Procaine hydrochloride	R

\* R = recovered; D = died.

necrotic bowel. It is somewhat surprising that infection with the gas bacillus organism is not more common, since it is usually present in large numbers when infarction of the bowel occurs; probably most of these organisms are avirulent forms.<sup>5</sup>

*Type and Location of Hernia.*—The relative frequency of the different types, classified on the basis of location, is shown in table 4. It

5. McIver, M. A.; White, J. C., and Lawson, G. M.: Ann. Surg. 89:647, 1929.

will be noted that more than one half of the strangulations occurred in inguinal hernias and about one-quarter in femoral hernias.

As shown in table 6, in over three quarters of the cases the small intestine alone was strangulated.

*Sex and Age.*—Among these cases there were one hundred males and forty-seven females. The average age of the patients was 44 years: six were infants under 1 year of age; more than two-thirds were over 40 years.

*Diagnosis.*—The diagnosis in cases of strangulated external hernia is usually obvious. In typical cases, a hernia that has previously been reducible becomes irreducible. This condition is accompanied by severe, often intense, pain, which may not be confined to the hernial sac but may take the form of generalized abdominal cramps. Vomiting is usually present, starting soon after the initial pain. Obstipation is present, although early in the illness the bowel below the point of obstruction may be emptied voluntarily or by means of an enema. If

TABLE 6.—*Location of Hernias*

Location of Obstruction	Cases	
	Number	Per Cent
Small intestine .....	127	86
Large intestine .....	7	5
Large and small intestines.....	13	9
Total.....	147	

the strangulation is not relieved, the symptoms increase in severity, and swelling of the hernial sac occurs, owing to exudate and edema. The late manifestations are those usually found in acute intestinal obstruction from any cause, namely, distention, fecal vomiting and prostration.

Although the diagnosis is usually easy, there are occasional cases in which it is not obvious. The patient may not be aware that he has a hernia, and a small, tense sac may be overlooked, particularly if it occurs in the femoral canal. In any patient with symptoms suggesting intestinal obstruction, the usual sites of hernia should be carefully examined to exclude the possibility of a small strangulated hernia. In this series there were three cases in which the diagnosis of strangulated hernia was not made until laparotomy had been performed and a knuckle of intestine found strangulated in the femoral canal.

*Operation.*—Anesthesia: The choice of an anesthetic is extremely important in cases of strangulated hernia. Although, as is well known, many patients can be operated on safely under ether, the great majority of patients can be operated on equally satisfactorily under local or spinal anesthesia. These types of anesthesia have a number of advan-

tages. The general depressant effect of ether is avoided; the reflexes are intact, so that there is no danger of aspirating foul vomitus (an accident that may constitute a serious complication with a general anesthetic), and peristalsis is not inhibited (it is, of course, actually stimulated by spinal anesthesia).

The various types of anesthetics used in this series are shown in table 7.

The largest number of operations were done under ether anesthesia, and, except in a small group done under nitrous oxide, the mortality was lowest in these cases. This means that in general the other types of anesthesia were used for patients coming late to operation and for those who from any standpoint were considered poor operative risks. The use of local anesthesia is particularly indicated in aged patients.

Any death following an operation for strangulated hernia in which a general anesthetic has been used should be carefully investigated to

TABLE 7.—*Type of Anesthetic Employed*

Anesthetic	Number of Cases	Number of Deaths	Mortality, per Cent
Ether.....	70	8	11
Nitrous oxide.....	5	0	0
Ethylene.....	3	1	33
Local*.....	62	16	25
Spinal.....	7	2	29
Total.....	147	27	18

\* In certain cases the local anesthetic was supplemented by a general anesthetic.

see if the outcome could have been avoided by the use of a local anesthetic.

**Operative Procedures:** In uncomplicated cases in this series the operative procedure consisted in cutting of the constricting ring, reduction of the contents of the sac and repair of the hernia.

In cases in which the intestine was found to be gangrenous at the time of operation, a variety of procedures was carried out, as shown in table 5. It will be noted that there were fifteen intestinal resections. In eight of these an immediate anastomosis was carried out; in seven, the ends of the intestine were brought out and the anastomosis reserved for a secondary operation; there were five deaths in each group. The decision as to which procedure is preferable in the individual case and to what extent the operation may justifiably be prolonged must rest on the judgment of the surgeon.

#### SUMMARY

1. One hundred and forty-seven patients with acute strangulated external hernias were operated on at the Massachusetts General Hospital from 1918 to 1927, inclusive.



2. Among these patients there were twenty-seven deaths, a mortality of 18 per cent. The highest mortality was among patients having umbilical or ventral hernias. One half of the deaths occurred in patients in whom symptoms of strangulation had existed for more than twenty-four hours.

3. There were nineteen patients in whom interference with the circulation was so marked that necrosis of the bowel occurred. Eleven of these patients died.

4. There were one hundred males and forty-seven females. The average age of the patients was 44 years. Six were infants under 1 year of age.

5. Local or spinal anesthesia is usually the method of choice, although for patients seen early a general anesthetic is frequently safe.

# CHRONIC ENDEMIC ERGOTISM

ITS RELATION TO THROMBO-ANGIITIS OBLITERANS

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Much has been written on the subject of thrombo-angiitis obliterans in recent years, particularly since Buerger's<sup>1</sup> first publication in 1908. There have been many theories as to the cause of this disease, among which bacterial infection and tobacco poisoning have predominated. Although bacteria have frequently been found in the vessels, they have not been constant or proved specific to thrombo-angiitis obliterans. Tobacco poisoning may have deleterious effects on sensitive vessels already the seat of organic changes and may be an important factor in precipitating acute attacks in chronic vascular diseases, such as the exacerbations in thrombo-angiitis obliterans and the anginal attacks in coronary disease. The initiation of organic vascular changes with thrombosis and gangrene has so far not been reproduced by tobacco poisoning.

Ergot, which has naturally been suspected to be the cause of thrombo-angiitis obliterans, has not been taken seriously in spite of the fact that it has for many years been known to produce organic vascular changes, thrombosis and ultimately gangrene. The failure to consider ergot more seriously in this disease may be because it has not been known to exist as a toxic contaminant of flour in the present day. Besides, other peculiarities required explanation, such as the occurrence of the disease most frequently in the young and in the middle-aged and in males of the Hebrew race. The relation of these peculiarities in thrombo-angiitis obliterans and ergotism (gangrenous form) was considered by me in an article<sup>2</sup> which covers in greater detail the etiology, toxicology and pathology of the two conditions.

## THE PRESENCE OF ERGOT

The terrible epidemics of ergotism have practically been extinct since the end of the last century, when the rye was heavily contaminated

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1. Buerger, Leo: Thrombo-Angiitis Obliterans: A Study of the Vascular Lesions Leading to Presenile Spontaneous Gangrene, *Am. J. M. Sc.* **136**:567, 1908.

2. Kaunitz, Julius: The Pathological Similarity of Thrombo-Angiitis Obliterans and Endemic Ergotism, *Am. J. Path.* **6**:299 (May) 1930.

with ergot. The absence of these epidemics is due to the more careful cleaning of the grain and the economic system, which results in the storage of grain for long periods. It is well known that the toxicity of ergot decreases with age. In spite of precautions and the economic systems, there have been small outbreaks of ergotism even in recent years. Robertson and Ashby<sup>3</sup> and Morgan<sup>4</sup> described such an outbreak occurring in Manchester, England, in 1927-1928. It is not so surprising that the periodic outbreaks occur as that they do not occur more often, considering the frequent ergot infection of the grain fields.

Since the ergot fungus attacks most of the grains and grasses, it is not strange that its presence is reported in most portions of the globe. As rye is the most susceptible host, it is natural to find this fungus most prolific in those regions in which rye occurs in the greatest abundance. It has been reported in every continent, including Australia and New Zealand. In North America it has been found in Vermont, Connecticut, New York, Michigan, Tennessee, Indiana, Wisconsin, Minnesota, Iowa, Kansas, Wyoming, Montana and other states, besides various places in Canada. Atanasoff<sup>5</sup> stated:

Grains, especially rye, in some seasons and in some fields are infected so heavily that nearly every head may have one or more sclerotia, as was reported from Wisconsin in 1917. Cases where 20 to 50 per cent of the heads were infected with ergot have been reported from various parts of the United States and Europe. The amount of ergot for 1917 in Connecticut ranged from 1 to 5 per cent. Decrease of the yield (of rye) by as high as 20 per cent has been reported from Russia (*as a result of ergot infection*).

Weniger,<sup>6</sup> writing of ergot infection in North Dakota, said:

In wheat and particularly in durum wheat, the disease has appeared and increased in severity in recent years. . . . In the epidemic of 1921 many fields of durum wheat were ruined by an early infection which resulted in nearly every head producing ergot bodies. . . .

Besides wheat and rye, one must remember that other grains, barley, corn and rice, may be contaminated by the ergot fungus.

Of other sources of the toxins there might be mentioned the human body, which elaborates the ergot-like substances, histamine and tyramine. These substances, like those obtained from ergot, may be of

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3. Robertson, James, and Ashby, Hugh T.: Ergot Poisoning among Rye Bread Consumers, *Brit. M. J.* **1**:302, 1928.

4. Morgan, M. T.: Report on an Outbreak of Alleged Ergot Poisoning by Rye Bread in Manchester, *J. Hyg.* **24**:51, 1929.

5. Atanasoff, D.: Ergot of Grains and Grasses, Monograph, U. S. Dept. Agric., Washington, 1920.

6. Weniger, Wanda: North Dakota Agriculture College, Agric. Exper. Sta., Bull. 176, April, 1924, p. 4.

pathologic importance. Since they are toxic in small doses, they should be given consideration as factors in the production of some of the vasomotor and trophic diseases as well as arteriosclerosis.

The importance of the ergot infection of the grain may be judged by the defensive measures used by the farmers against the fungus as well as the methods employed in separating the ergot from the grain. It is admitted that it is impossible to remove all the ergot. When the contamination is heavy, the flour will naturally contain more ergot in spite of all efforts to remove it from the grain. In the Manchester outbreak mentioned, the grain was milled and sold to the bakers without having first removed the ergot or allowed the grain to age. The flour contained approximately 1 per cent of ergot and produced symptoms in some persons sufficiently acute and characteristic to arouse the suspicions of the physicians as to the cause. In the earlier epidemics it was not unusual for the flour to contain from 20 to 50 per cent ergot. The resultant disease was very acute, overwhelming most of the population.

Just how much ergot is necessary to produce thrombo-angiitis obliterans and other of the vasomotor and trophic diseases is not known. It may be that small quantities taken over a long period give rise to these disturbances, the ergot poisoning being lost track of because of the mildness of the intoxication and the insidious onset of the later manifestations.

#### VASOMOTOR AND TROPHIC DISEASES

There is a group of vasomotor and trophic diseases of unknown origin in which may be mentioned Raynaud's disease, erythromelalgia, acro-asphyxia, acroparesthesia, multiple neurotic gangrene, scleroderma, sclerodactylia and dermatomyositis. In an article<sup>7</sup> correlating this group of diseases with ergotism, I also included thrombo-angiitis obliterans, because of its also manifesting some of the vasomotor and trophic disturbances as this group. There are some other conditions that should also be mentioned for consideration, such as paroxysmal hemoglobinuria and epilepsy, both of which have been described as occurring in ergotism and Raynaud's disease. Lenticular cataracts have been described as occurring in ergotism. Some cases of cataracts occurring in young people might be traced to ergotism. Hauswirth and Eisenberg<sup>8</sup> recently described peptic ulcers as being commonly associated with venofibrosis. The ulcerations are probably trophic manifestations of the vascular condition. The hyperacidity might be considered a vasomotor manifestation.

7. Kaunitz, Julius: Chronic Endemic Ergotism: Its Relation to the Vasomotor and Trophic Diseases, *Arch. Int. Med.* **47**:548 (April) 1931.

8. Hauswirth, Louis, and Eisenberg, Arthur A.: Disseminated Venofibrosis (Phlebosclerosis), *Arch. Path.* **11**:857 (June) 1931.

One hesitates to attempt the unification of these vascular and trophic disturbances that have been so carefully classified as separate entities. Classification dependent on symptomatic and even pathologic differences, however, should not interfere with a unification dependent on a common cause. A difference in the lesions might depend on a difference in the ergot toxin and the idiosyncrasy of the host. Marked contrasts in pathology, clinical manifestations and distribution occur in many diseases. Such marked differences as between miliary tuberculosis and lupus vulgaris in tuberculosis make one realize that as a result of such a complex drug as ergot such dissimilar conditions as thrombo-angiitis obliterans and scleroderma might be obtained.

#### SUSCEPTIBILITY

*Nationalities.*—In studying the nationalities and races affected with thrombo-angiitis obliterans, one finds that although the disease is almost universal in its distribution, it is most prevalent in people of those countries in which rye bread is the staple article of diet, generally in the northern Slavic countries: Russia, Poland, Ukraine, East Prussia, etc. Most of the cases reported by Buerger,<sup>9</sup> Jablons<sup>10</sup> and Brown and Allen<sup>11</sup> were in persons of these nationalities. Buerger, who is responsible for most of the literature and investigations of this disease, believed it to be peculiar to the Jewish race. In his large series of cases in New York City the patients were almost exclusively Jews. Jablons reported 90 per cent Jews in a series of 200 cases in New York City. He mentioned Idelson, who reported 60 per cent Jews in a series of 226 cases from Poland, Lithuania and East Prussia. In a large series of cases, which included native Americans, Norwegians, Swedes, Finlanders, Germans, Austrians, Chinese, Japanese, Koreans, Turks, etc., reported by the various authors and compiled by Brown and Allen, slightly more than 50 per cent occurred among Jews. One cannot deny that of the reported cases thrombo-angiitis obliterans occurs predominantly in Jews. The explanation is found in the fact that these people take their physical ailments more seriously and make their disease known. Many individuals of a more phlegmatic people, less sensitive or more indifferent to the condition, do not bother to visit the surgeon and so leave unreported a large number of cases of thrombo-angiitis obliterans in non-Jews. An

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9. Buerger, Leo: *The Circulatory Disturbances of the Extremities*, Philadelphia, W. B. Saunders, 1924.

10. Jablons, Benjamin: *Thrombo-Angiitis Obliterans*, Internat. Clin. **3**:192, 1925.

11. Brown, George E., and Allen, Edgar V.: *Thrombo-Angiitis Obliterans*, Mayo Clinic Monograph, Philadelphia, W. B. Saunders, 1928, p. 27.

exaggerated instance of such indifference is Ludlow's<sup>12</sup> description of this disease among the Koreans, some of whom amputated their own toes. One would naturally agree with him that thrombo-angiitis obliterans must be more prevalent in this race than his 40 cases indicate. It is impossible to estimate the number of such people who never visit surgeons and so preclude the reporting of their disease. There are probably many unreported cases in the Slavic and other countries in which the grain is heavily infected with ergot. It is also to be borne in mind that in the outlying districts where most of the peasants live the cases may not be reported because the disease is not recognized. Even in the larger centers of the United States the disease is frequently treated for rheumatism, flatfoot, etc.

It is safer to say that more cases of thrombo-angiitis obliterans have been reported in Jews than to say that it is peculiar to this people. In considering their susceptibility to this disease, it is significant that it is very rare in the descendants of native Jews of the United States and England whose dietetic habits are different from those of the Slavic Jews. It is interesting to note that in the small ergot epidemic mentioned in Manchester of 276 cases, all occurred in Jews. The disease was more pronounced in those coming from Russia, Poland and Germany than in English-born Jews. It seems more rational to regard the susceptibility as one depending on habits and susceptibility peculiar to the individual, rather than to any racial idiosyncrasy.

*Sex.*—Of 500 cases reported by Buerger, 3 cases occurred in females. In Jablons' 200 cases, 1 per cent occurred in females. Idelson<sup>13</sup> reported 14 women in a series of 358 cases. The greater susceptibility of males to thrombo-angiitis obliterans is very evident from these figures. One can find a parallel here in the susceptibility to the gangrenous form of ergotism which affected the males to the greatest extent. In 68 epidemics of ergotism, according to Krysinsky,<sup>14</sup> the gangrenous form affected, with one exception, the males exclusively. The convulsive form affected the women, children and the aged. Renaudin<sup>15</sup> stated that the gangrenous form of ergotism does not affect females. Tessier<sup>16</sup> observed that

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12. Ludlow, A. I., quoted by Brown and Allen (footnote 11).

13. Idelson, H.: Ueber die Claudicatio intermittens und deren Beziehungen zu Allgemeinerkrankungen nebst pathologisch-anatomischen Untersuchungen, Deutsche Ztschr. f. Nervenhe. 80:321, 1928.

14. Krysinsky, Stanislaus: Pathologische und kritische Beiträge zur Mutterkornfrage, Jena, Gustav Fischer, 1888.

15. Renaudin: Ergotisme, in Dictionnaire des sciences médicales, Paris, Crapart & Panckoucke, 1815, vol. 8; quoted by Neale, Adam, in: Spur or Ergot of Rye, London, H. Phillips, 1828, vol. 8, p. 18.

16. Tessier, Abbe: Traité des maladies des graines, Paris, 1783, vol. 8; quoted by Neale, Adam, in: Spur or Ergot of Rye (footnote 15).

spurred rye acts with less force on females. Noel,<sup>17</sup> surgeon at Hotel Dieu of Orleans, describing the epidemic of 1710, said of ergot: ". . . attacks men by preference . . . what is most astonishing, does not attack women."

What is true of epidemic is also true of medicinal ergotism. In spite of the tremendous quantity of ergot consumed in this country<sup>18</sup>—170,000 to 264,000 pounds yearly—one rarely hears of a case of gangrene in women. It is interesting to note that even in fowls one encounters an increased susceptibility in males. Gittinger and Munch,<sup>19</sup> in an assay of ergot by the cock's comb method, found that the hens had no value, their combs showing slight blanching or no effect whatever, while, of the control, 90 per cent of the cocks gave satisfactory results.

It is not within the realm of this paper to consider why certain diseases are limited to one or the other sex. For my purpose it is pertinent that both thrombo-angiitis obliterans and gangrene ergotism have a preference for the male sex.

*Age.*—Thrombo-angiitis obliterans occurs most frequently in young and in middle-aged men. In epidemic ergotism, the gangrenous form, according to Krynsky, occurred most frequently in young and in middle-aged men.

*Social Class.*—Thrombo-angiitis obliterans occurs principally among the laboring classes. This was also found true of epidemic ergotism. The explanation given was that rye bread, which was the cheapest form of food, was the principal article of their diet.

#### DIET

As the chief article of diet in the north Slavic countries is rye bread, it is most natural that the patients coming from those countries should admit eating rye bread. It is also natural for the poor laboring classes, who make up the largest proportion of the cases of thrombo-angiitis obliterans to be big consumers of this cheapest form of food. Those patients whom I questioned admitted eating large quantities. From one half to three quarters of a pound of rye bread during a meal was not considered unusual. Rye bread, as one knows, was also the universal diet of the patients afflicted with epidemic ergotism. Those who ate liberally of meat, milk and cheese suffered less severely, or not at all. The addition of meat and milk to the diet of people who consume large

17. Noel, quoted in Raynaud, Maurice: *On Local Asphyxia and Symmetrical Gangrene of the Extremities*, translated by Thomas Barlow, *Selected Monographs*, London, New Sydenham Society, 1888, p. 130.

18. United States Department of Commerce, private communication.

19. Gittinger, G. E., and Munch, J. C.: *Assay of Ergot by the Cock's Comb Method*, *J. Am. Pharm. A.* **16**:505, 1927.

quantities of maize serves to prevent the occurrence of pellagra. This additional diet of meat and milk foods may serve in a similar way to neutralize the toxins of ergot. Those people who eat much rye bread might be advised with profit to add meat and milk to their diets. It might be of interest here to note that Pentschew,<sup>20</sup> by feeding ergot to apes, produced, in spite of a diet containing a liberal quantity of vitamins, lesions comparable to those of pellagra.

It is well known that large quantities of rye bread are consumed by the Germans, yet there are relatively few cases of thrombo-angiitis obliterans reported by them. It may be that they are more careful in selecting and cleaning their grain, or perhaps their more varied diet helps to prevent the disease. Another element to consider is the preparing of the bread. In the Salvic countries a sour bread is made of rye flour leavened with old rye dough instead of yeast. The dough is allowed to ripen each time for several days. It takes much longer than with yeast. A small quantity of dough is always saved for the next baking. It is possible that a rye flour rich in ergot might develop larger quantities of the so-called putrefactive substances, such as histamine and tyramine, if allowed to stand for a long time. The Germans are not as partial as their Slavic neighbors to this sour rye bread.

To explain the occurrence of thrombo-angiitis obliterans in the Chinese, Japanese and Koreans from the standpoint of ergotism, one would have to know more about the diet of these people. It may be that their rice had been infected with ergot. In the more northern districts of China, where rice does not grow, rye bread forms a large part of the diet.

One occasionally meets persons who deny having eaten rye bread. This does not mean that they may not have eaten some ergot-infected grain such as wheat, particularly durum wheat. Barley, rice and corn have also been found infected with ergot. Corn smut, which like ergot causes a bluing of the cock's comb, requires further investigation.

Individual effects depend to a great extent on the dosage. Very large doses, such as are consumed during ergotism epidemics, overwhelm most of the population. Very small quantities occurring in grain today affect only the very susceptible, otherwise there would be many more cases of ergotism. Susceptibility to small doses may to some extent depend on the slowness of elimination. A constipated person, for example, who is subjected to the prolonged action of a small quantity of ergot may be affected more than one who ingests a large dose of ergot but who eliminates it very rapidly. Many of the Jewish patients whom I examined admitted being habitually constipated.

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20. Pentschew, Angel: Experimentelle Untersuchung über Pellagra, Ergotismus und Bleivergiftung, *Krankheitsforschung* 7:415, 1929.



The possibility that in intestinal stasis some ergot is converted into its putrefactive components, histamine and tyramine, so enhancing its toxicity, deserves more than a passing consideration. Guggisberg<sup>21</sup> showed that these amines are only found in old ergot. These putrefactive amines are normally found in the intestinal tract, and their relationship to the abnormal intestinal condition is therefore doubly important. The possibility of these amines being an etiologic factor in the vascular diseases, including arteriosclerosis, was mentioned.

#### SYMPTOMATOLOGY

For the symptoms of gangrenous ergotism one is forced to rely on the reports of the epidemic form, since the reports on the endemic form are practically limited to the medicinal intoxications. After the acute symptoms, such as headaches, vomiting, cramps, diarrhea, etc., agonizing pains appear, generally in the legs. These pains, which are said to penetrate the limbs like fire, both precede and accompany the gangrene. The limb becomes livid, which in some cases is preceded by an erysipelatous blush. The cyanosis passes into darkness and blackness, and finally gangrene, which may be either dry or moist, generally the former. One notes here symptoms suggesting vasomotor as well as organic changes in the vessels. Some of the sensory symptoms may result from anoxemia as well as neural changes.

The artery is felt to tighten from day to day, and the pulse becomes very small, until finally it is imperceptible. Among the sensory symptoms mentioned are formication, anesthesia, coldness, heat and pain. Tonic contractions of the legs are also mentioned. There may be pallor, rubor or cyanosis of the toes, fingers or limbs. Gangrene may follow months after the initial intoxication.

The chief symptoms of thrombo-angiitis obliterans are burning or cramplike pains, usually in the calf of the leg. Fatigue in the leg frequently precedes these pains in the condition termed intermittent claudication. There is generally present paresthesia, anesthesia, formication, coldness or heat. There may be pallor, cyanosis or rubor. When the affected leg is elevated, it immediately becomes bloodless, but soon changes from pallor to the original redness or cyanosis when placed in the pendant position. There are trophic changes to be noticed in the skin and nails of the fingers or toes affected, to which may be added ulceration and gangrene. Occlusion of the artery is essential to the diagnosis of thrombo-angiitis obliterans. The symptoms occur in some cases long before the complete thrombotic occlusion. This is particularly true of the vasomotor and sensory symptoms and suggests the possibility

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21. Guggisberg, Hans: Beitrag zur Sekalfrage, Zentralbl. f. Gynäk. 53:578, 1929.

of recurrent spastic contraction of the diseased vessels. Vasomotor symptoms, such as rubor, cyanosis and pallor, which are common in thrombo-angiitis obliterans, may be due to a hyperirritability of both the vessels and the nerves that control them. The good effect obtained by lumbar ganglionectomy is an argument for the presence of an irritability of the sympathetic nerves. The nerves and vessels, which may be in an irritable state as a result of earlier intoxication, may also be kept in this state by the frequent introduction of small quantities of the specific toxin.

A résumé of the symptoms would indicate that in both ergotism (gangrenous form) and thrombo-angiitis obliterans one finds symptoms of vasomotor and trophic disturbances. In both conditions there are pallor, rubor and cyanosis; anesthesia, paresthesia, severe pains in the extremities, principally the lower, imperceptible pulse, trophic changes, edema, ulceration and ultimately gangrene.

Through the courtesy of Dr. Samuels at the German Polyclinic, I have recently had an opportunity to try the effects of ergot on a few patients having thrombo-angiitis obliterans.

Because the cases are too few in number and the ergot was given guardedly, it is impossible to draw any definite conclusion. The results are only mentioned with the hope of stimulating others in this branch of the problem.

It can be said that the symptoms of these patients were definitely aggravated by the drug. Objectively, the plantar regions and palms became reddened or cyanotic. One case resembled erythromelalgia, the redness of the soles of the feet continuing for a week after ergot was discontinued. The oscillometer showed drops of from 1 to 2.5 (Pachon). Subjectively, symptoms common to both thrombo-angiitis obliterans and ergotism, such as pains, paresthesia, anesthesia and weakness in the limbs, were renewed or aggravated.

Although the positive effect of ergot in these cases is no causal proof of thrombo-angiitis obliterans, it is, however, important, because a negative result could have been interpreted as a denial.

The toxicologic effects of ergot suggest the possibility that this substance may be the cause of the symptoms of thrombo-angiitis obliterans. Several substances are found in ergot, chiefly ergotamine, ergotoxine, and the previously mentioned putrefactive substances, histamine and tyramine. Ergotamine, ergotoxine and histamine, which are powerful uterine contractors, produce capillary dilatation by inhibition of the motor sympathetic nerves. Tyramine is a powerful arterial constrictor. Histamine also has this property, but to a lesser extent. The action of these substances that contract the arteries and dilate the capillaries results in all types of vasomotor and trophic disturbances such as pallor,

rubor and cyanosis of the extremities. Prolonged action leads to stagnation with anoxemia in the peripheral circulation, the resulting cyanosis becoming more intense or black, followed by gangrene.

One is tempted to speculate on the different vasomotor and trophic disturbances possible, depending on the varying quantities of ergotamine, histamine, tyromine and other substances present in the ergot.

One of the roosters to which I fed ergot for a period of four months continued to have edema and vasomotor disturbances of the comb three months after the last dose of ergot. At autopsy there were signs of endarterial hyperplasia, but no obliterating thrombus to account for the edema. The comb showed variations in color from day to day, being most frequently pale at the base and blue at the tips, illustrating arterial constriction with capillary dilatation. It seems reasonable to believe that the injurious effects of the toxins left the vessels and their nerves hypersensitive to their environment. Such permanent hyperirritability resulting from an intoxication is perhaps of great significance, as it may explain the hypertonic state of the vessels in thrombo-angiitis obliterans and other conditions, such as arteriosclerosis. In the latter condition the vessels probably become hyperirritable soon after being damaged by some severe infection or intoxication, such as scarlatina. The usual pressor substances found in the body, such as epinephrine, pituitary histamine and tyramine, which do not disturb the normal vessels, may produce a severe spastic condition in these vessels. This hyperirritability to the pressor substances is one of the explanations of hypertension in arteriosclerosis, the progressiveness of the disease probably depending on the continuous vascular spasm. In thrombo-angiitis obliterans, the initial ergot intoxication might also be responsible for an angio-spastic condition, the result of vascular damage.

#### COURSE

The course of thrombo-angiitis obliterans is generally very chronic, lasting in some cases many years. It is not known how soon the intoxication occurs before the symptoms. In ergotism, symptoms of gangrene have been noticed to occur several months after the original intoxication. Intercurrent diseases, such as typhus or pneumonia, and vasomotor irritants, such as cold weather, may precipitate an attack of gangrene. Tobacco was considered in the introduction. Buffum<sup>22</sup> noticed in horses gangrene with sloughing of the tails and hooves to occur two years after the original ergot intoxication. If such late manifestations occur in human beings it is not strange that the original intoxication is lost sight of. Such may also be a possibility in thrombo-angiitis

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22. Buffum, B. C.: Grasses and Forage Plants, Wyoming Agric. Exper. Sta. Bull. 16, p. 223; quoted in Atanasoff (footnote 5, p. 90).

obliterans. It is possible that susceptible persons, by daily feeding of bread slightly infected with ergot, do not experience the acute manifestations of ergotism but later develop the chronic manifestations of thrombo-angiitis obliterans.

#### PATHOLOGY

Only some of the salient features of the pathology of thrombo-angiitis obliterans will be described here. For details on this subject, Brown, Allen and Mahorner,<sup>11</sup> Buerger<sup>9</sup> and Ramirez<sup>23</sup> are recommended.

The lesions of thrombo-angiitis obliterans are generally found in the extremities and occasionally in the viscera. They are in part due to neurotrophic disturbances and vascular occlusion which leads to infarction. The typical lesions are found in the blood vessels, which become thickened with obliteration of their lumina. The veins are often the seat of acute thrombophlebitis. This acute venous inflammation and thrombosis led Buerger to apply the name thrombo-angiitis obliterans to this disease. It was his opinion that the disease began with an acute inflammation and thrombosis of the vessels. Earlier authors, Friedländer,<sup>24</sup> and some of the more recent authors, Ramirez and Mahorner, believe that thrombosis is secondary to an intimal proliferation. The latter believe that even the acute thrombophlebitis of this disease is a superimposed condition, other vascular changes having preceded it.

The theory of the gradual narrowing of the lumen by the encroaching thickening intima is more consonant with the gradual impairment of the circulation noticed in this disease. An acute inflammation accompanied by a sudden thrombosis in the artery would produce very acute local manifestations with gangrene at the outset of the disease before collateral circulation could be established.

It is a question whether it is wise to draw definite conclusions of the pathogenesis in the arteries from the findings in the acutely inflamed veins. Acute arterial inflammation is relatively rare, whereas acute phlebitis is common. This is not so surprising when one realizes that the veins, particularly of the extremities, receive tribute directly from the superficial tissues, frequently the seat of infection.

Bacteria have frequently been found in thrombo-angiitis obliterans but so far none have been found specific to this disease. In the absence of this evidence and the fact that the patients rarely have any of the constitutional symptoms of bacterial disease, one should seriously consider as a cause an intoxicant capable of inducing the pathologic changes of this disease.

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23. Ramirez, Alexandro: *Étude critique sur l'anatomie et la pathogénie des artérites oblitérantes juvéniles des membres et de la soi-disante maladie de Buerger*, Paris, Thèse, 1927.

24. Friedländer, Carl: *Ueber Arteriitis obliterans*, *Centralbl. f. d. med. Wissensch.* 14:65, 1876.

In following the pathologic progress in the vessels one might suggest that an initial intoxication by injury or only severe excitation results first in a contraction and thickening of the walls with an intimal hyperplasia. The second phase is the clot which becomes attached to the intimal process. Both this intimal process and the red clot undergo organization and often fuse so thoroughly as to make one fibrous mass. One is then unable to distinguish with any certainty intima from thrombus. Fibrosis and hyalinization are frequently found here and in the media.

As organization takes place in the lumen, the vessel wall would become impoverished unless some compensatory circulation were established. Small vessels are formed in the occluding fibrotic mass and media to offset the impaired circulation. These new vessels are one of the characteristics of the later phases of the disease.

Arteries are frequently found with their accompanying veins and nerves adherent to the adjacent structures. These nerves are frequently found to be denser on account of the increased connective tissue. Many of the nerves are found in a state of degeneration. This is attributed to the ischemia and is not correlated with any cerebrospinal changes. Whether the cerebrospinal tract is affected by this disease is not known, as no autopsy report of its investigation exists.

#### PATHOLOGY OF ERGOTISM

Unfortunately, information on the pathology of ergotism is very meager. One is familiar with the textbook's description of a contraction and thickening of the vessel wall and a thrombosis of the lumen followed by gangrene of the extremity. Dr. Mitchell Bruce<sup>25</sup> said that the posterior columns of the cord show sclerosis. In the constricted and thrombosed arterioles a glutinous matter is found, and the vessels either primarily or secondarily undergo hyaline degeneration, especially of the tunica intima.

As in thrombo-angiitis obliterans, the visceral vessels may also be affected. Perhaps the most detailed pathologic report on ergotism in human beings is the one by Vinogradoff<sup>26</sup> on the epidemic of acute convulsant ergotism that occurred at Viatka in 1889. Only the viscera were found affected, principally the liver, kidneys and spleen. Nearly all the large vessels of these organs contained thrombi. Some were red and others contained fibrin with scattered erythrocytes. In smaller

25. Bruce, Mitchell, quoted by Allbutt and Dixon, in Allbutt and Rolleston: *A System of Medicine*, New York, The Macmillan Company, 1906, vol. 2, part 1, p. 889.

26. Vinogradoff, N. F.: *K patologicheskoi anatomii rafanii*, *Vrach* 16:585, 622 and 647, 1895.

branches of the portal vein organized thrombi were found. Some vessel walls were thickened, their lumina narrowed to such an extent as not to permit more than two or three erythrocytes to pass. Marked intimal proliferation was observed in some vessels. Many of the vessels had undergone fibrosis or hyaline degeneration. In spite of the more acute lesions described in these cases of ergotism, it is possible to correlate

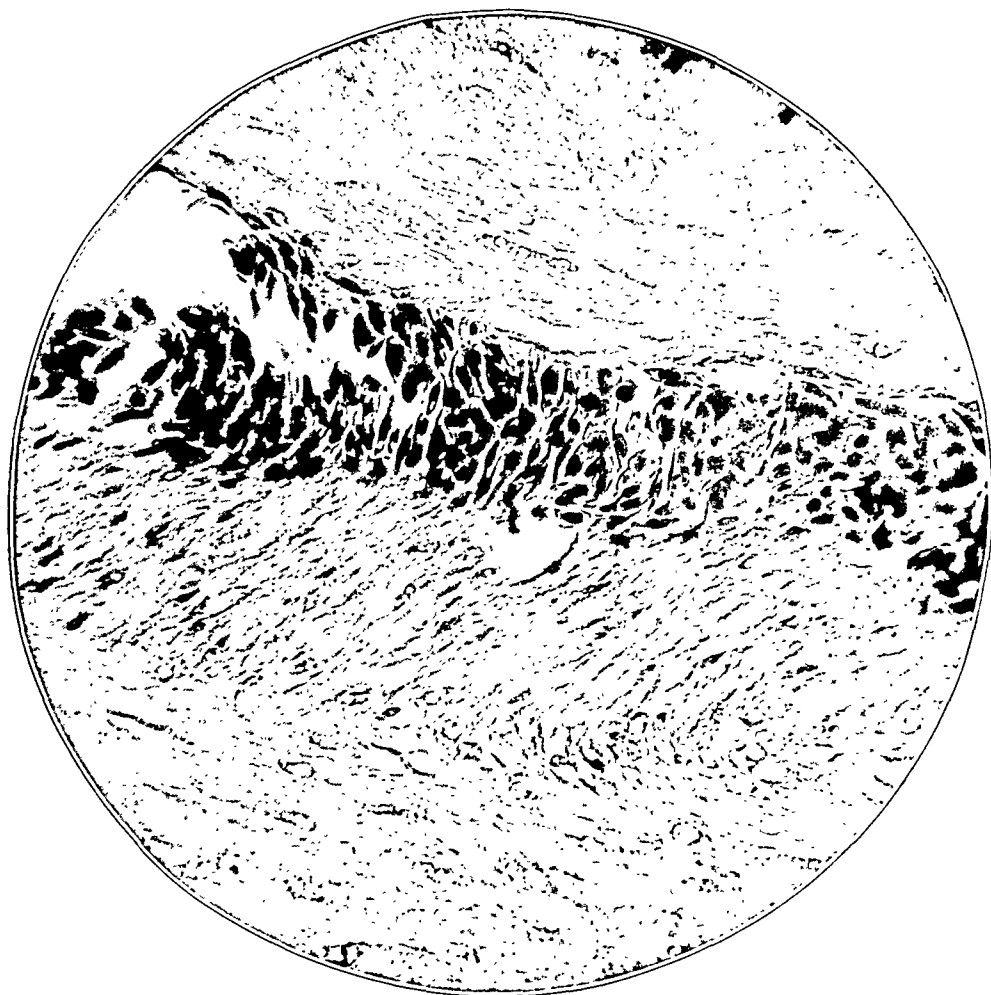


Fig. 1.—Chronic ergotism (about one year). Section of a vessel taken from the middle of the posterior portion of the cock's comb. Early hyperplasia of the intima is evident, the cells tending to grow with their long axes radial, as in thrombo-angiitis obliterans. The oval cells in the lumen are erythrocytes, which are nucleated in birds.

some of the vascular changes with those occurring in thrombo-angiitis obliterans, particularly the thickened intima and the red and organized thrombi.

One of the roosters to which I fed ergot for almost a year had some vascular lesions comparable with thrombo-angiitis obliterans, showing first an early stage (fig. 1) in which the intimal proliferation

was marked, the cells tending to arrange themselves with their long axes radially as in thrombo-angiitis obliterans, and secondly a more chronic vascular lesion (fig. 2) in which a thrombus had become attached to the thickened intimal process. The thrombus and intima fused and became organized as in thrombo-angiitis obliterans to make one fibrous mass. In another rooster, ergot was fed eight months and then dis-



Fig. 2.—Chronic ergotism, simulating thrombo-angiitis. This section was obtained about 2 mm. proximal to the one shown in figure 1. This vessel shows the later stages in which the hyperplastic intima and the attached thrombus have undergone organization and fused into one indistinguishable mass. It is interesting to note an early and a late process coexisting in ergotism as in thrombo-angiitis obliterans.

continued for six months. It was resumed at the end of this time with the purpose of producing an acute exacerbation in a chronic ergotism. In this case, the vessels of the comb showed all types of acute and chronic vascular lesions. One of them is shown in figure 3, containing an obliterating thrombus. Canalization of the thrombus, as in thrombo-

angiitis obliterans, appears to have been reproduced. From the same rooster another vessel (fig. 4) is shown, to illustrate acute ergotism superimposed on a chronic ergot condition. The thickened hyaloid intima is shown to exhibit a circumscribed inflammatory area extending into the lumen. The inflammation, which has the ear-marks of an infection, is solely due to ergot intoxication. It is not unusual in thrombo-

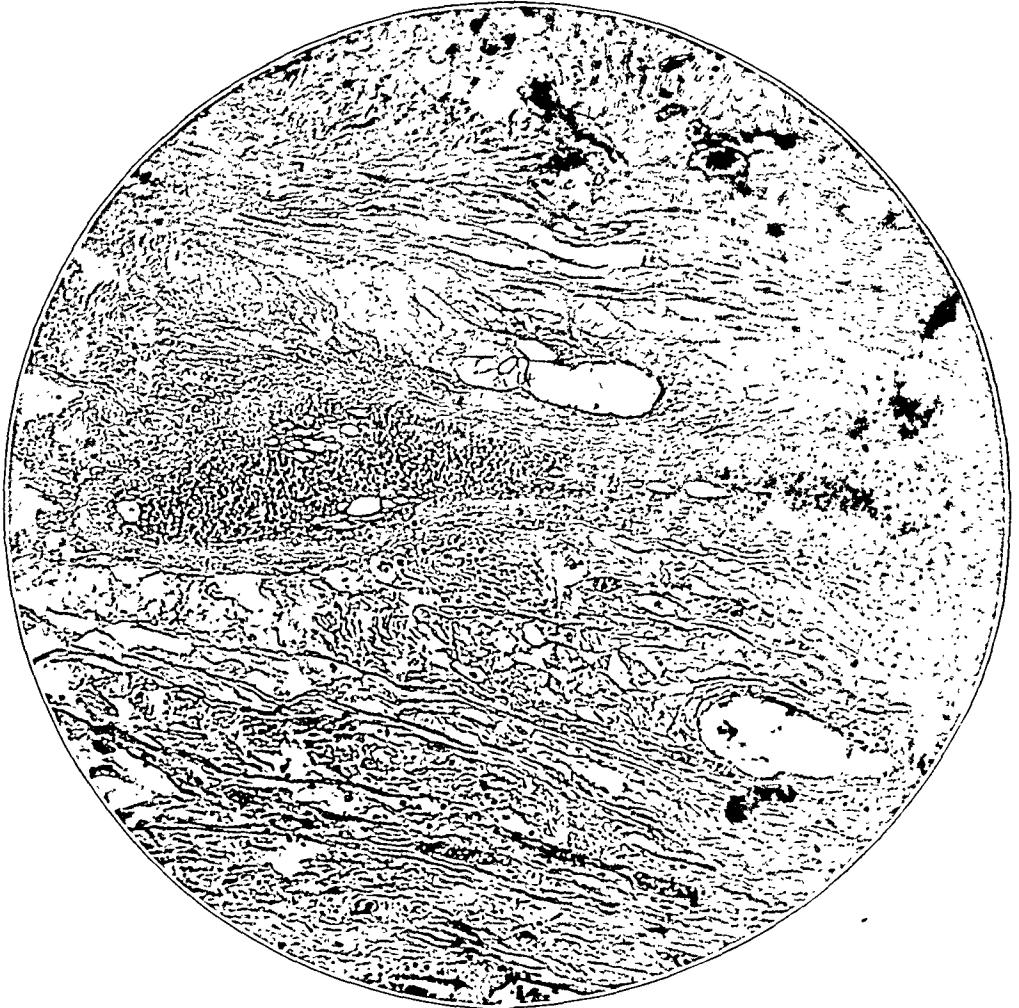


Fig. 3.—Chronic ergotism (about sixteen months). This section was obtained from one of the tips of the cock's comb that showed vasomotor changes, necrosis, etc. The vessel wall shows a chronic hyaline degeneration of the muscularis and intima. The lumen, however, contains an obliterating red thrombus which appears canalized, indicating an acute process superimposed on a more chronic one.

angiitis obliterans to find a recent clot in a vessel already the seat of an old organized thrombus, the latter, like the intimal thickening, predisposing the lumen to further thrombosis. It is well, however, to keep in mind that the same toxic substances that result in early intimal hyperplasia and thrombosis may, when later introduced into the body, bring about a repetition of the pathologic results. In the epidemics of ergot-



ism it was noticed that toward spring, as the ergot lost its force, an abatement of the symptoms occurred, the symptoms reappearing in the late fall and winter. Although it is very likely that the return of the symptoms was due to the reingestion of fresh ergot of the recent harvest, which is most toxic, it might here be repeated that the original damage in the vessels from the first ingestion of ergot caused a hyperirritability



Fig. 4.—Chronic ergotism (about sixteen months). This section was obtained from a branch of the right carotid artery from the same rooster as figure 3. The intima and muscularis have undergone hyaline degeneration. In the intimal process can be seen a circumscribed inflammatory area extending into the lumen. This area, which has the appearance of an infection, is an example of the toxic effects of ergot.

and so predisposed them to further damage, the cold of the winter months adding interference to the already embarrassed peripheral circulation.

Vascular stasis, which enhances thrombus formation, is itself enhanced by the pathologic changes in the lumen of the vessel. Ergot, as has been seen, is capable of producing vascular stasis.

## CONCLUSIONS

The etiology, symptomatology and pathology of ergotism are to a great extent simulated by thrombo-angiitis obliterans.

Both ergotism and thrombo-angiitis obliterans are practically limited to young and to middle-aged persons of the male sex.

Females are rarely affected by either ergotism or thrombo-angiitis obliterans.

The Jews, who regard their ailments seriously, are more apt to seek medical advice, and in consequence have their cases reported. This may, in part, explain why more cases of thrombo-angiitis obliterans have been reported in this people.

The symptoms of both thrombo-angiitis obliterans and ergotism include many of the symptoms found in the vasomotor and trophic disturbances, obliteration of the pulse and gangrene being some of the ultimate results in both conditions.

The pathology of ergotism has some characteristics in common with thrombo-angiitis obliterans. In both one finds early as well as organized intimal proliferation of the vessels, which may be the seat of early, red and late organized thrombi. These may cause complete obliteration of the vessels.

The diet in both thrombo-angiitis obliterans and ergotism includes to a great extent rye bread. There is ample proof that this bread is frequently contaminated with ergot, occasionally in toxic doses.

Greater precautions are advisable in cleaning and aging of all the grains susceptible to ergot infection, principally rye and wheat, particularly durum wheat. There is no need to prove the pathogenicity of ergot, for its toxic nature is well recognized clinically as well as experimentally.

Pathologic effects suggestive of various vasomotor and trophic diseases have been produced by experimental ergotism in cocks. Fresh and organized thrombi and organization of the thickened tunica intima was obtained. In one of my more recent experiments, vessels were obtained with obliterating canalized thrombi, simulating thrombo-angiitis obliterans.

Since very small doses of ergot may be capable of aggravating the condition of a vessel already diseased, it might be found advisable for patients with thrombo-angiitis obliterans to forego rye bread which has not been proved to be free from ergot.

Histamine and tyramine, commonly found in the human body and in ergot, should be carefully investigated as to their prolonged effect on the vessels, as they may be responsible for some of the vascular conditions under consideration.

# TUBERCULOSIS OF MECKEL'S DIVERTICULUM

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It is well said that medical and pathologic curiosities often become of sufficient importance to be considered of practical interest. It is certain that the list of complications arising in Meckel's diverticula is daily becoming a larger and more impressive compilation. Over twenty-seven years ago, Porter<sup>1</sup> collected 184 cases of Meckel's diverticula exhibiting pathologic complications. Since that time there has been a steady and rapid rise in the reported cases, with complications ranging from ulcers of the mucosa with perforation (heterotopia of the gastric mucosa) to primary bizarre neoplasms.

Previously reported by Ruysch<sup>2</sup> in 1701, it remained for Meckel,<sup>3</sup> in 1809, to describe more fully this congenital remnant and to further the theory of its origin in the remains of the omphalomesenteric duct. According to Christie,<sup>4</sup> this pouch is encountered in about 1 per cent of all persons, and is seen in the proportion of 75 per cent males to 25 per cent females. By far the greater number of complications have occurred in males. In the Mayo<sup>5</sup> series of 10,000 laparotomies, 33 per cent of Meckel's diverticula encountered exhibited certain pathologic changes.

In reviewing the literature on this particular complication of tuberculosis, eight authentically reported cases have been cited. In 1871, Concato<sup>6</sup> described a diverticulum of the Meckel type complicated by tuberculosis. In 1873, Dixon<sup>7</sup> reported the postmortem discovery of a generalized peritonitis due to perforation of tuberculous ulcers of a Meckel's diverticulum. Italo Antonetti,<sup>8</sup> in 1902, cited a case occurring in a man, 20 years of age, in which a long diverticulum of the lower ileum was complicated by tuberculosis. Resection of the diverticulum

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1. Porter, M. F.: Abdominal Crises Caused by Meckel's Diverticulum, J. A. M. A. **45**:883 (Sept. 23) 1905.

2. Ruysch, F.: Thesaurus Anatomicus, VII, Amsteloedami, J. Wolters, 1707.

3. Meckel, J. F.: Arch. f. d. Path. **9**:428, 1809; Tabulæ anatomico-pathologicae modos omnes quibus partium corporis humani omnium forma externa atque interna a norma recedit, exhibentes, Leipzig, J. F. Gleditsch, 1817-1826.

4. Christie, A. U.: Am. J. Dis. Child. **42**:544 (Sept.) 1931.

5. Balfour: J. Minnesota M. A. **21**:110, 1911.

6. Concato, quoted by Wirtz: Inaugural Dissertation, University of Bonn, 1919.

7. Dixon, quoted by Porter,<sup>1</sup> p. 889.

8. Antonelli, Italo: Riv. veneta d. sc. med. **36**:87, 134, 322, 422, 474, 1902; **37**:80, 162, 269, 315, 361, 465, 514, 1902.

was followed by recovery. In 1908, Fitz<sup>9</sup> reported a case of Meckel's diverticulum in which there were several ulcerations of a tuberculous nature, apparently unruptured. Later the same year, Thompson<sup>10</sup> reported the recovery of a woman with a diverticulum the wall of which was studded with many tubercles. This diverticulum was resected, with favorable results. In another case cited by Burkhardt,<sup>11</sup> the patient complained of symptoms suggesting intestinal obstruction. Laparotomy was performed and a tuberculous diverticulum was resected; this was followed by relief of symptoms, though the patient died of miliary tuberculosis at a later date. In 1918, Wirtz<sup>12</sup> noted at autopsy a small diverticulum of the Meckel type covered with many small miliary tubercles. In 1925, Coley<sup>13</sup> excellently abstracted the literature on this subject, and cited his case, which occurred in a young man. Resection of the diverticulum was followed by improvement, but the patient died of pulmonary tuberculosis two months after operation.

#### REPORT OF CASE

*History.*—E. P., a white American, aged 30 years, entered Peralta Hospital on Sept. 18, 1931, complaining of vague intestinal symptoms and marked weakness. The past history was of interest in that he had had pneumonia accompanied by pleural effusion when he was a child and influenza in 1918, and an appendectomy had been performed in 1926. The family history was irrelevant. For two years previous to hospitalization he had been subject to occasional, intermittent, cramp-like pains, which were especially noted in the upper and lower quadrants of the right side. Four months previously he passed a small amount of bright blood rectally, and since then had noticed tarry stools on frequent occasions. The weight, although varying from time to time, was not an index of any serious disease process, and the state of nutrition was maintained. He had no suggestive symptoms of pulmonary disturbance and none of the usual subjective evidence of tuberculosis.

*Examination.*—Physical examination revealed little of value, save that there was definite tenderness in the right quadrants. Examination of the chest gave no indication of an active lesion of the lungs. The usual routine laboratory examinations gave negative results, but during the complete roentgenographic gastric and colonic series a constriction was seen in the transverse colon near the hepatic flexure, which was thought to be neoplastic.

*Operation and Course.*—An exploratory laparotomy was performed on Oct. 25, 1931, and an annular constriction was found in the region of the hepatic flexure coinciding with that seen in the roentgenographic studies. In addition, there was a large edematous mass in the region of the ileocecal junction, and the proximal small intestines were enormously dilated. An ileostomy was performed, and a

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9. Fitz, R.: *Edinburgh M. J.* **23**:120, 1908.

10. Thompson: *Edinburgh M. J.* **23**:120, 1908.

11. Burkhardt: *München. med. Wchnschr.* **29**:1652, 1914.

12. Wirtz: *Inaugural Dissertation, University of Bonn, 1919*; quoted by Coley (footnote 13).

13. Coley, B. L.: *Tuberculosis of Meckel's Diverticulum Associated with Tuberculous Appendix, Arch. Surg.* **11**:519 (Oct.) 1925.

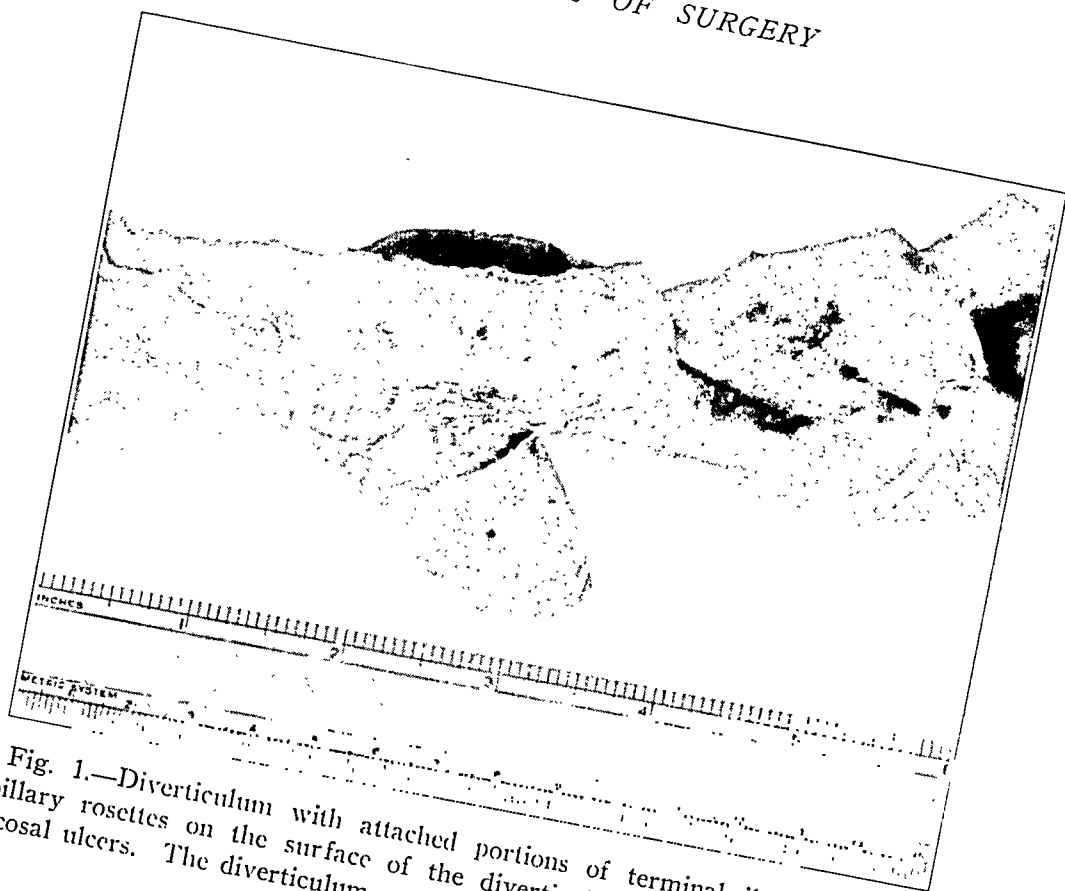


Fig. 1.—Diverticulum with attached portions of terminal ileum. Note the capillary rosettes on the surface of the diverticulum, indicative of underlying mucosal ulcers. The diverticulum presents oral inclination.

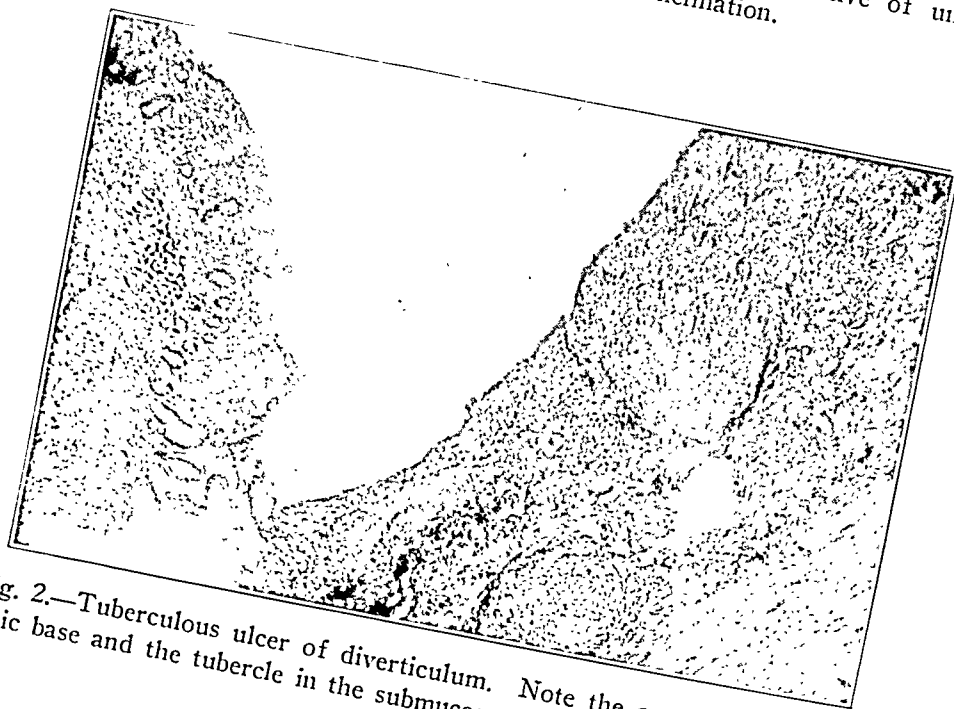


Fig. 2.—Tuberculous ulcer of diverticulum. Note the overhanging edges, the necrotic base and the tubercle in the submucosa.

resection was planned for a later date. Beyond this the abdomen was not disturbed. Frozen section taken from the periphery of this mass revealed chronic granulation tissue. The patient experienced a stormy postoperative course and died five days later.

*Postmortem Examination.*—Gross Observations: Only abdominal necropsy was performed immediately after death, and certain interesting features were encountered. Approximately 200 cc. of free, turbid fluid was seen in the abdominal cavity, giving evidence of a generalized peritonitis (a culture showed *B. coli*). The lesions at the hepatic flexure and the ileocecal junction were tuberculous. The most interesting feature, however, was a diverticulum of the lower part of the ileum, approximately 50 cm. from the ileocecal junction. It was 5 mm. in length, and the tip was adherent to the parietal peritoneum. Examination of the wall showed numerous tuberculous ulcers, one of which had perforated, allowing the escape of intestinal contents into the abdominal cavity. One of the ulcers had become penetrating in that it had become adherent to the parietal peritoneum, and as a result the proximal ileum had become acutely flexed around this fixed point, causing obstruction. The ileum proximal to this point had become gangrenous for a distance of 40 cm., and presented a fibropurulent exudate over the peritoneal surface.

Microscopic Observations: The microscopic sections from representative lesions of the diverticulum presented many recent tubercles composed of proliferating epithelioid cells, groups of lymphocytes and occasional giant cells. The surrounding tissues exhibited a diffuse infiltration of polymorphonuclear neutrophilic leukocytes. The ulcers were essentially typical of tuberculosis, showing overhanging edges, bases displaying marked necrosis and numerous tubercles scattered through the submucosa. Search of the specimen failed to reveal evidence of displaced gastric mucosa.

#### COMMENT

This case is of unusual interest in that three pathologic and complicating features are encountered in the study of a Meckel's diverticulum, namely, tuberculosis, intestinal obstruction and perforation resulting in generalized peritonitis. The perforation and acute obstruction evidently occurred after operative intervention, but the tuberculous ulcers had been present for some time. There was no evidence of tuberculous enteritis when the appendix was removed in 1926, but the process probably had been in progress for two years. Primary tuberculosis occurring in a Meckel's diverticulum is apparently unknown; it is seen rather as a secondary lesion coincident with the disease elsewhere in the body. Moreover, it intensifies and complicates the general picture of an otherwise simple tuberculous enteritis, precipitating symptoms ending in some acute abdominal crisis. Tuberculosis of Meckel's diverticulum is usually an inflammatory lesion of the enteroperitoneal type, exhibiting characteristics of both proliferative and ulcerative processes. It is interesting to note that none of the cases reported showed heterotopia of the gastric mucosa. Realizing the relative resistance of the stomach to tuberculosis one would be led to surmise that such a heterotopia phenomenon in a diverticulum would lend an additional immunity to an infection of this type. In five of the eight

cases reported previously, operation was performed, with relief of symptoms. Three of the five patients were reported cured after two years; the other two died soon after surgical intervention from generalized tuberculous infection.

#### SUMMARY

1. A case in which there are the essential features of a Meckel's diverticulum complicated by tuberculosis is presented; this report constitutes the ninth authentic instance in the literature.

2. In this patient, as in the other cases reported, a fairly well advanced stage of tuberculous enteritis, with secondary involvement of the diverticulum, was present.

3. Resection is the therapy of election when such a procedure is possible, especially if the condition is complicated further by obstructive symptoms.

# CIRCULATION OF THE HUMAN THYROID

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The gross blood supply of the thyroid gland is a matter of common knowledge, but the finer details of the circulation are not well described. There are certain facts about the vascularity of this organ that make for difficulty in demonstration and description. The thyroid is said to have the richest blood supply of any organ in the human body. This high degree of vascularity is well illustrated in the figures given by Burton-Opitz.<sup>1</sup> In his chart for the volume of blood per minute per hundred grams of organ, the thyroid heads the list. It receives 560 cc. of blood per minute per hundred grams. This is from two to ten times the quantity given for other organs. Such a great volume per minute can be possible only in the presence of a rich capillary bed. This highly vascular character provides such a complex network of vessels as seen in the specimens into which injections have been made that they are difficult or impossible to interpret. X-ray pictures of specimens perfused with radiopaque masses show only the larger vessels because of the rich capillary circulation and also because the colloid is not well penetrated by the x-rays.

The macroscopic blood supply of the thyroid gland is very well described in all present day systems of anatomy. Briefly it is as follows: 1. The superior thyroid artery is the first branch of the external carotid artery and is divided into (*a*) the infrahyoid artery to the regional muscles, (*b*) the sternomastoid artery, (*c*) the superior laryngeal artery to the mucosa and the intrinsic muscles of the larynx, (*d*) the cricothyroid artery and (*e*) the glandular arteries including a large lateral and anterior branch, a medial and superior branch and a small branch which dips into the gland. 2. The inferior thyroid artery is the largest branch of the thyroid axis; it passes medially to the posterior surface of the lateral lobes near the inferior pole and divides into (*a*) the muscular branches to the scalenus anterior and the inferior constrictors, (*b*) the ascending cervical artery to the deep neck muscles and the ver-

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From the Department of Pathology of the University of Oregon Medical School, Portland, Ore.

Submitted as a senior thesis in the Department of Surgery in the fulfilment of graduation requirements.

1. Burton-Opitz, R.: Quart. J. Exper. Physiol. 4:117, 1911.



tebral arteries, (c) the inferior laryngeal artery and (d) the glandular arteries, which are rather inconstant but include the ascending branch, which passes upward on the posterior surface to supply the regional thyroid and parathyroids, and a small branch to the inferior portion of the isthmus. 3. The thyroidea ima, which usually arises from the innominate artery and passes to the inferior surface of the isthmus, may also be a derivative of the common carotid, the subclavian or the internal mammary arteries.

These large branches of the thyroid artery are a real problem, as there are profuse peripheral anastomoses with adjacent structures. This may be due in part to the fact that the large vessels do not dip deep into the gland but spread out over its surface, sending in smaller branches. Mastin,<sup>2</sup> in his consideration of the surgical significance of the blood supply of the thyroid gland, emphasized the anastomoses of the larger vessel. He found that the superior thyroid artery and the homolateral inferior thyroid artery communicated directly in 100 per cent of the cases. The two superiors or one superior and a contralateral inferior anastomosed in 80 per cent of the specimens. Direct communications between all vessels occurred in 20 per cent of the instances. The homolateral anastomosis is very well developed and is seen on the lateral and posterior surface of each lobe. That of the contralateral vessels is ill developed and varies markedly. Major<sup>3</sup> quoted Landstrom and Strecheisen's conclusions that the anastomoses occur on the surface of the thyroid and not only between homolateral vessels but also between contralateral ones. From a large series of specimens into which injections were made, Delore and Alamartine<sup>4</sup> reached similar conclusions.

In addition to the direct communications in the circulation of the thyroid, there are definite indirect anastomoses. According to Mastin,<sup>2</sup> these are formed by the following channels: (1) the indirect laryngeal anastomosis through the superior laryngeal artery communicating with the cricothyroid branch of the superior thyroid artery; (2) a similar connection between the superior and inferior laryngeal arteries; (3) the tracheal plexus of vessels which is formed by the junction of the inferior laryngeal and the inferior thyroid arteries with the anterior mediastinal branches of the internal mammary arteries and the bronchial arteries, and (4) another possibility, the communication of the contralateral inferior laryngeal and the ascending pharyngeal arteries, about the esophagus. In addition there is a fifth group of rather ill defined indirect channels made up of variable branches from the superficial trunks that extend out into the muscles and fascia about the gland. It is this indirect system of anastomoses together with the larger more

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2. Mastin, E. V.: *Surg., Gynec. & Obst.* **36**:69 (Jan.) 1923.

3. Major, R. H.: *Am. J. Anat.* **9**:475, 1909.

4. Delore, X., and Alamartine, H.: *Rev. de chir.* **44**:391, 1911.

direct communications that render it difficult to make complete vascular casts and particularly hard to fill the deep capillary bed.

The thyroid veins are large, communicate freely, and are numerous. According to Mastin,<sup>2</sup> they are double and start in superficial bar anastomoses. This does not correspond with the description given in different texts on anatomy. These usually describe superior, middle and inferior thyroid veins. The superior thyroid vein accompanies the corresponding thyroid artery, passes over the common carotid and empties into the lingual or internal jugular vein. The middle thyroid vein starts in the lower portion of the lateral lobes of the thyroid, is joined by the laryngeal and tracheal veins, then empties into the lower part of the internal jugular vein. The inferior thyroid artery is not accompanied by a corresponding vein. There are inferior thyroid veins, however. These are usually multiple (from two to four), having their origin in the venous plexus on the surface of the thyroid gland and communicating freely with the middle and superior thyroid veins. The left one passes in front of the trachea, behind the sternomastoid muscle, communicates with its fellow by transverse branches and empties into the left innominate vein. The right one takes a similar course and empties into the right innominate vein. These veins receive esophageal, tracheal and inferior laryngeal tributaries and are supplied with valves at their terminations.

The microscopic circulation is not as well defined as the gross. Most authors refer to it in a very general way without giving one a very definite conception of the nature of the acinar vessels. There are a few specific references made to the capillaries about acini. Mastin<sup>2</sup> stated that the interlobar vessels break up into a capillary network that lies just beneath the acinar epithelium. More detail is given by Schafer,<sup>5</sup> who believes that the arterioles terminate in a capillary bed about the alveolus, each of which has an arteriole and venule. These vessels are in close contact with the epithelium, and according to him, may project between the cells. Rienhoff,<sup>6</sup> in his study of the gross and microscopic structure of the human thyroid gland, did not specifically mention the capillary bed. He did, however, show one illustration of an individual acinus in which the vessels stood out faintly in relief. The only other demonstration found was a drawing of an injected specimen of the capillaries about an acinus of a dog's thyroid, given by Schafer.<sup>5</sup>

In view of the lack of any definite demonstration of the acinar vessels of the human thyroid, it seemed advisable to attempt to study this part of the circulation further. After reviewing the many methods of study-

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5. Schafer, A. E., in Quain: *Elements of Anatomy*, New York, Longmans, Green & Co., 1912.

6. Rienhoff, W. F.: *Contrib. Embryol.*, 1929, no. 123, p. 99.

ing the circulation, by injection masses, the method employed by Gross<sup>7</sup> for the injection of hearts was selected. Essentially it is the perfusion of the arteries with a warm barium sulphate-gelatin mixture, which is opaque to the roentgen rays. It soon became evident that this would not be a satisfactory method for the thyroid, because of the greater vascularity and the opacity of the colloid. The failure of this method left two other possibilities, the casting of the vessels with subsequent digestion or reconstruction with serial sections. In 1923, Hinman, Morison and Lee-Brown<sup>8</sup> published the results of injecting celloidin, acetone and camphor solutions into the renal vessels. After injections were made

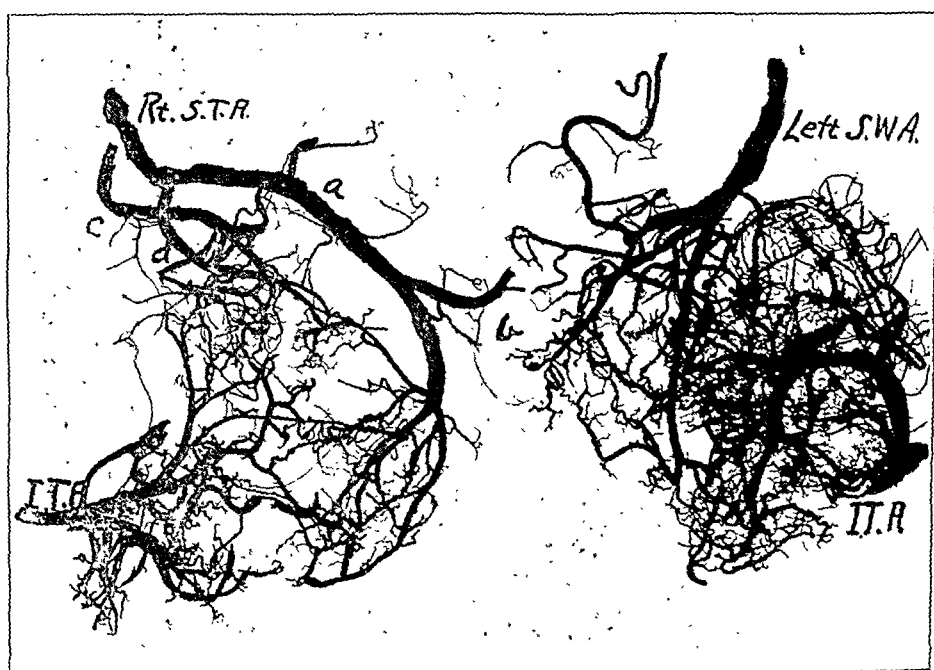


Fig. 1.—Photograph of celloidin cast of the larger thyroid arteries, taken by transmitted light. *Rt.S.T.A.* indicates the right superior thyroid artery; *I.T.A.*, the inferior thyroid artery; *a*, the largest branch running medially down to the isthmus; *b*, rich anastomosis between the two superior thyroid arteries; *c*, the lateral branch slightly displaced in mounting; *d*, the parenchymal branch, the only one that dips into the substance of the thyroid.

into these organs in the fresh state and the injection material was hardened in cold water, the surrounding substance was digested away, leaving the cast of the circulation. This method was found suitable for injections of the thyroid gland.

7. Gross, Louis: *The Blood Supply of the Heart*, New York, Paul B. Hoeber, Inc., 1921.

8. Hinman, Frank; Morison, D. M., and Lee-Brown, R. K.: *Methods of Demonstrating the Circulation in General*, J. A. M. A. **81**:177 (July 21) 1923.

## EXPERIMENTAL WORK

The materials used to carry out this method were: mercury manometer reading to 500 mm., large bore needles, air pressure apparatus capable of regulation and two acetone-celloidin solutions. One thin solution was used for the small vessels and a thick solution for the large ones. Fresh glands were used, and these were not dissected out but removed with the surrounding muscle and fascia. If these structures are removed, injection is practically impossible because of the many open vessels. In

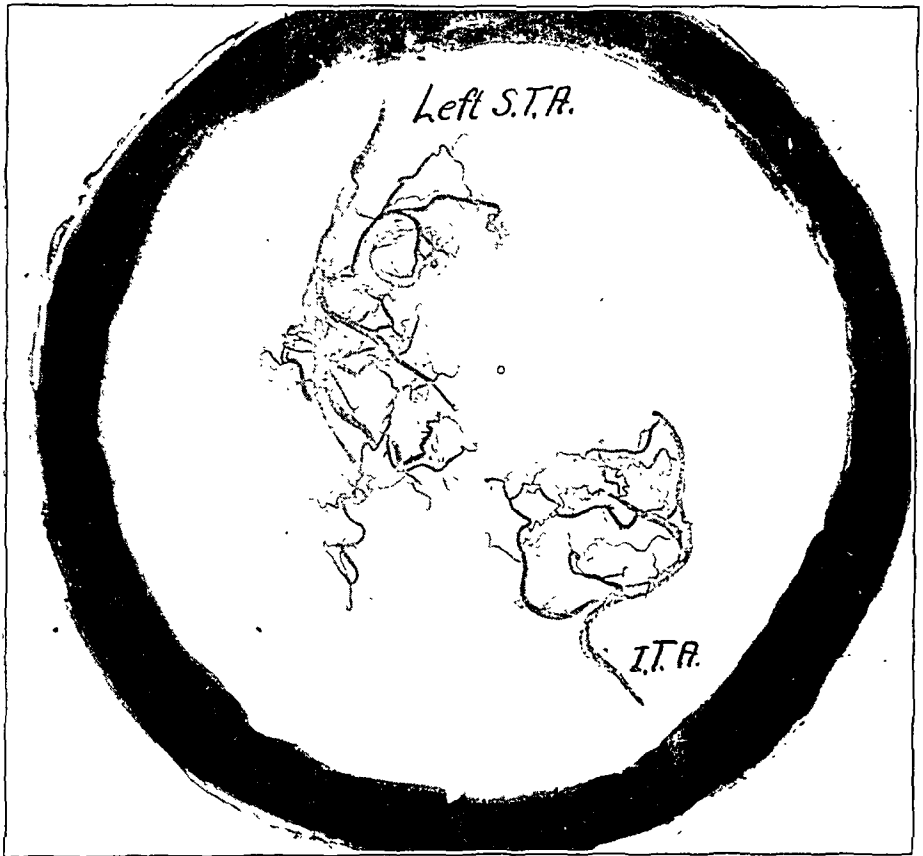


Fig. 2.—The superior and inferior thyroid arteries were separated in this case to show the relative distribution of each vessel.

such a case the injection mass runs out over the surface of the gland rather than into the deep vascular bed. Fixed or embalmed organs cannot be digested even in 75 per cent hydrochloric acid; accordingly glands were selected from the bodies of persons soon after death to avoid postmortem changes and the coagulation of blood in the vessels. The vascular bed was washed with physiologic solution of sodium chloride to dislodge the clots and moisten the vessel walls. The thin celloidin was injected with pressures up to 350 to 400 mm. of mercury. The celloidin solution consisted of 3 Gm. of celloidin and 2 Gm. of cam-

phor in 100 cc. of acetone. With this thin mass attempts were made to fill the capillaries and arterioles. Next, the thick celloidin was forced in to fill the larger vessels. This solution was made of celloidin or washed x-ray films, 10 Gm., and camphor, 8 Gm., in acetone 100 cc. The specimen into which injection was made was allowed to set in cold water for twenty-four hours, the parenchyma was then dissolved away with 75 per cent hydrochloric acid, and washed and neutralized in dilute sodium hydroxide. The procedure is not as simple as it is in an organ with a hilus, capsule and single or closed blood supply, for the thyroid with

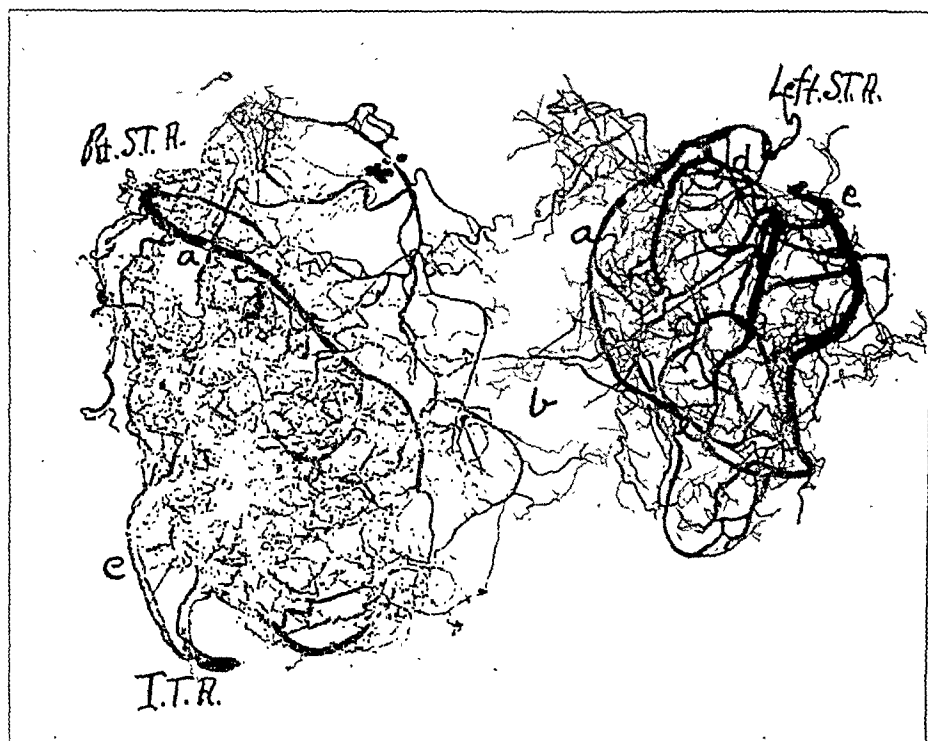


Fig. 3.—Photograph of the celloidin cast of the larger thyroid arteries taken by transmitted light. *Rt. S.T.A.* indicates the right superior thyroid artery; *Left S.T.A.*, the left superior thyroid artery; *I.T.A.*, the right inferior thyroid artery. An injection was not made into the left inferior thyroid artery. *a*, *b* and *c* are the same as in figure 1. The right lobe in this case shows the density of the arteries and arterioles better than is seen in figure 1.

four or five arteries, profuse anastomoses and many small vessels to the surrounding structures is difficult to make injections into.

To deliver the injection mass to the four main arteries at equal pressure requires complicated apparatus that becomes obstructed easily or bursts under the high pressures required. However, several fairly good casts were obtained by this method. These are not complete, for few capillaries can be seen, and in many the arterioles are not evident. In general, the distribution of the larger vessels was found to be essentially as given in the previous descriptions. The superior thyroid artery was

found to supply roughly the superior, anterior and medial portion including the isthmus (fig. 2). There is little difference in the size of the two vessels, but judging from the specimens obtained by injection, the inferior thyroid artery was larger in children and very old persons. In practically all instances, the superior thyroid artery was seen to send its largest branch downward, anteriorly and medially along the edge of the lateral lobes to the isthmus where it joined its fellow of the opposite side. This anastomosis was usually found to be a direct communication of

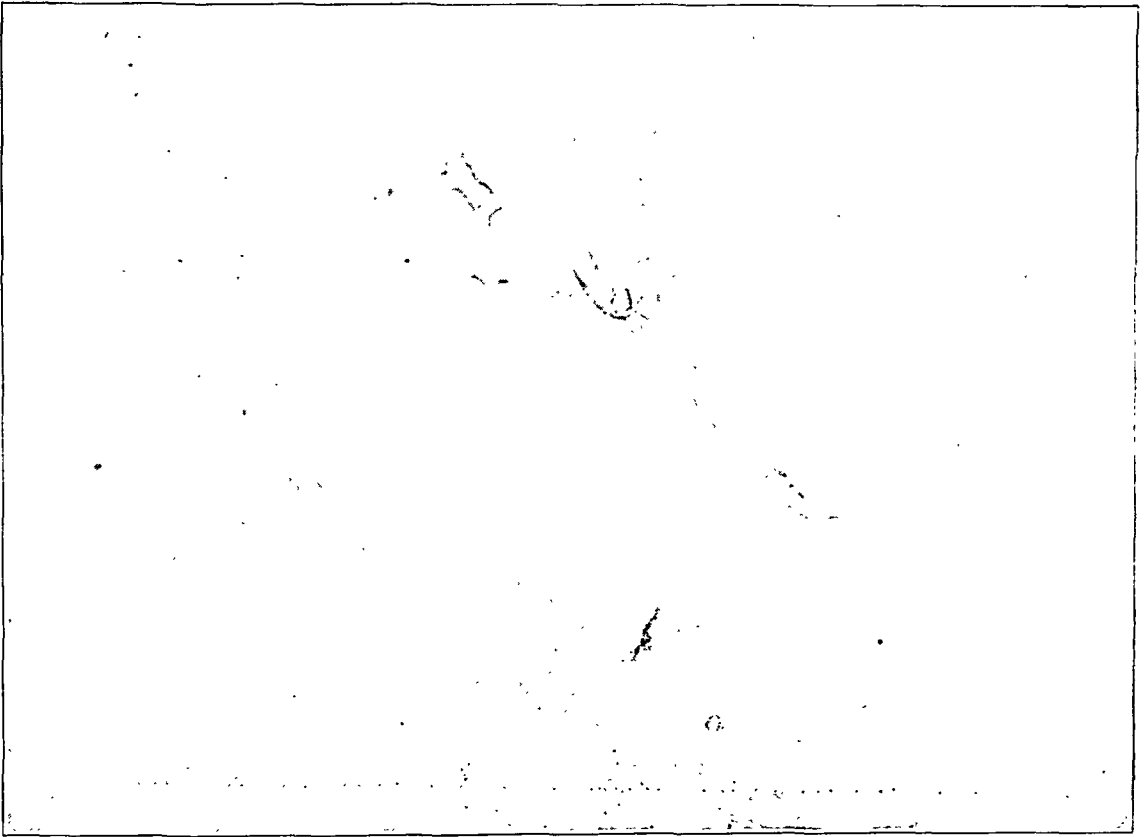


Fig. 4.—Photomicrograph of the small branches of the thyroid artery showing the expanding funnel-shaped end of one of the intralobular vessels. Only a few of such fine vessels could be found in the casts studied. Most of the casts present only a treelike branching of vessels with little tendency to uniformity. Such vessels were larger than the ones seen here. The size and shape of this termination corresponds well to an acinus.

large vessels. This vessel then turned downward and often supplied the medial portion of the inferior pole (figs. 1 and 3). Several such casts were obtained, but cannot be included here. The anterior marginal and parenchymal branches are also shown in these figures. The inferior thyroid artery was found to be quite variable, but in general it sent large branches posteriorly and laterally with only small branches to the anterior portion of the inferior pole (figs 1 and 3).

## COMMENT

Many other casts were made but were not wholly satisfactory. These specimens did reveal certain things, however. The size of the arteries varied somewhat according to the age. In children and elderly persons, the inferior thyroid arteries were more prominent than the superior. Mastin<sup>2</sup> measured a large number of thyroid arteries and found that the diameter of the inferior thyroid artery averaged 0.9 mm. greater than the superior. In many specimens spherical defects were found, and often nodules of friable digested gland fell from them. Such findings undoubtedly indicated that an adenoma had been present at this point and no infiltration of its blood supply had occurred. This failure of infiltration corresponds well with the necrosis and degeneration found grossly as evidence of poor vascularity.

The gross and microscopic study of the casts discloses a certain degree of uniformity of structure. The large arteries have been



Fig. 5.—Photograph of a cast of the blood vessels of the hog thyroid gland taken by reflected light. The detail is obscured due to the abundant fine capillary bed superimposed on the larger vessels. In this case better casts were obtained because the hog thyroid is a single lobed structure in the loose fat of the neck and it has a hilus with one artery and vein. This simplifies the injection, affording complete casts of the entire vascular tree.

described in detail previously. The secondary branches do not show well in the photographs so they must be traced by the use of the microscope. These secondary branches have been called parenchymal arteries and are the ones that dip into the substance of the thyroid. Within the gland there is a treelike branching of them, forming the interlobular vessels which pass between the lobules in the connective tissue septums described by Rienhoff.<sup>6</sup> Each interlobular artery divides into several intralobular arterioles, which extend between the individual acini. These vessels are supported by a scant stroma. Many such vessels have been traced to this point, but few casts contain the terminal capillaries shown in figure 4. The structure of these vessels is best studied under high power magnification. Although the acini are not present within the

terminal branches, the concavity within these formations corresponds very well with the size of the individual acinus. The casts of the hog thyroid (fig. 5), which are more complete owing to the simple blood supply, show the terminal branching much like the partially flexed fingers of the hand. The intralobular vessels, when viewed through the high power lenses, are seen to end in a clublike process from which extend from four to six slender branches representing capillaries. The distribution of these terminal strands corresponds well with the size and shape of the acini of the hog thyroid. In both the hog thyroid and the human thyroid, the casts present no structures beyond those described. Judging from the size and uniformity of structure, these probably represent the periacinar capillary bed.

The branches of the thyroid arteries may be summarized as follows: main thyroid artery, parenchymal arteries, interlobular arteries, intralobular arterioles and periacinar capillaries.

#### CONCLUSIONS

1. The accepted gross blood supply of the thyroid gland is presented.
2. The casts of the thyroid arteries obtained by the celloidin-acetone technic demonstrate the general circulation as well as the intrinsic capillary bed.



## A REVIEW OF UROLOGIC SURGERY

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*(Concluded from page 1010)*

### CONSERVATION IN RENAL SURGERY

Barney<sup>29</sup> stated that even though one good kidney or a portion of it is sufficient to maintain health, an attempt should be made to conserve as much tissue as possible. However, a kidney which, because of infection or some other condition, will be a menace to the patient should not be saved. Nephrectomy may be the most advisable procedure in one case; in another almost identical case conservative measures may be satisfactory. Conservative measures are not applicable to new growths or to tuberculosis; nephrectomy is indicated in these conditions. In other pathologic conditions, such as pyonephrosis, trauma and congenital deformity, conservation is also often contraindicated.

Nephrotomy has been practically abandoned in the treatment of renal calculi. Rosenow reviewed 1,767 cases of nephrotomy with a mortality of 5.89 per cent and 950 cases of pyelotomy with a mortality of 0.7 per cent. In an investigation of the results of nephrectomy for stone, undertaken by Barney, it was found that stones were overlooked in the kidney as often after nephrotomy as after pyelotomy. Recent advances in the technic of operation for renal calculi include the use of the fluoroscope and actual roentgenogram on the table at the time of operation.

At one time immediate nephrectomy was usually done in cases of acute and serious coccal infections of the kidney. At the present time it is realized that these intense and fulminating infections will generally

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29. Barney, J. D.: *Conservative Surgery of Kidney*, Pennsylvania M. J. **35**: 155 (Dec.) 1931.

subside spontaneously under palliative and supportive treatment and with careful observation. If operation eventually is indicated, simple decapsulation with drainage will usually relieve the condition.

Aberrant renal vessels occur frequently, are often bilateral and are the cause of many cases of hydronephrosis or pyonephrosis. They cannot be readily detected before operation except by a process of elimination. The drainage with which they have interfered must be reestablished; infection, if present, must be cleared up, and the renal tissue must be kept intact if nephrectomy is not a necessity. In many cases, after study of the situation found at operation, the position of the kidney can be changed by various modifications of a nephropexy procedure, so as to prevent further interference with drainage by the aberrant vessel.

Plastic operations on the ureteropelvic juncture have been performed since 1880. Although many successful cases have been reported, they are generally unsatisfactory and ureteropyeloneostomy is preferable. Plastic operations on or plications of the greatly dilated renal pelvis are often essential features to a satisfactory result in these cases and are frequently combined with ureteral transplantation.

Heminephrectomy is one of the conservative operations that must be considered in at least a small number of cases.

Conservatism may be used in a large percentage of cases of rupture of the kidney by trauma. Although immediate nephrectomy may sometimes be necessary, expectant treatment is applicable in most cases.

A technic in the expectant treatment of pyelitis of pregnancy has been developed so that abortion or surgical interference with the kidney is seldom necessary. After normal termination of the pregnancy, the infection usually subsides, leaving the kidney in practically a normal state.

Careful and thorough preoperative study of cases is necessary in renal surgery. An understanding of a condition prior to operation often leads to correct diagnosis and insures a better plan of procedure and more facility in its performance.

#### URETER

*Tumor.*—MacKenzie and Ratner<sup>30</sup> stated that 59 cases of primary tumor and 8 cases of metastatic tumor of the ureter are reported in the literature, to which they add 3 cases. Secondary invasions by direct extension from adjacent structures are not considered metastatic. The presence of metastasis is proved by the demonstration of malignant cells in the perivascular lymph spaces or blood vessels of the ureter.

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30. MacKenzie, D. W., and Ratner, Max: Metastatic Growths of the Ureter: A Brief Review of the Literature and a Report of Three Cases. *Brit. J. Urol.* 4:27 (March) 1932.

The patient in the first case died of cardiac failure and renal insufficiency. At necropsy adenocarcinoma of the prostate gland with metastasis in both ureters was found, producing bilateral pyonephrosis. In the second case, the primary tumor was scirrhous adenocarcinoma of the stomach with metastasis to the right ureter and right pyonephrosis. The patient in the third case had carcinoma of the uterine cervix. The kidney was examined because of pain in the left loin and dysuria, and obstruction in the middle of the abdominal portion of the left ureter and infection of a hydronephrotic sac on the left were found. At operation carcinoma was found at the juncture of an incomplete reduplication of the left ureter in its upper third.

In all of the cases malignant cells were demonstrated in the perivascular lymph spaces or blood vessels about the ureters, proving the metastatic nature of the growth. There are no pathognomonic signs or symptoms of this condition, and the diagnosis is usually made at operation or by postmortem examination.

Melicow and Findlay<sup>31</sup> reviewed the reported cases of primary benign tumors of the ureter. Primary nephrectomy was performed in 7 cases with only 1 satisfactory result. Complete nephro-ureterectomy was performed in 9 of the cases. It was done in only 4 of the 18 operative cases as a primary procedure; in 5, it was done in several stages. There was no operative mortality among the patients so treated. It is Melicow and Findlay's belief that, if a tumor of the ureter can be definitely diagnosed and the opposite kidney is functioning satisfactorily, primary nephro-ureterectomy is the operation of choice. The extent of the tumor is seldom known before operation or at operation, and other growths may be omitted from the removal if only a portion of the ureter is extirpated.

The authors cited in detail a case of primary benign neoplasm of the ureter accompanied by stricture of the ureter, ureteral and renal calculi, and marked dilatation and infection of the renal pelvis and ureter, a combination of lesions which has never been reported in the literature.

*Stone.*—Crance<sup>32</sup> reported a series of 77 cases of calculi in the ureter, in 3 (3.89 per cent) of which ureterolithotomy was required, in 72 cases (93.5 per cent) stones were passed successfully without open operation, and in 2 cases stones have not been passed. A method of removing the ureteral catheters during irrigation has given good results

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31. Melicow, M. M., and Findlay, H. V.: Primary Benign Tumors of the Ureter: Review of Literature and Report of a Case, *Surg., Gynec. & Obst.* **54**: 680 (April) 1932.

32. Crance, A. M.: *The Diagnosis of Ureteral Calculi and the Problem of Their Conservative Management*, *Am. J. Surg.* **15**:120 (Jan.) 1932.

in most cases. As the catheters are about to be withdrawn, one is plugged (if there are two) and a 30 cc. syringe is filled with sterile water and connected to the catheter. The kidney is filled slightly beyond the point at which the patient feels renal pressure. The catheter is slowly withdrawn with one hand, and the syringe is held for injection in the other hand. The traction caused by the downward motion of the catheter, plus the force from above, gives satisfactory results in many instances. Frequently following this procedure stones have been passed within forty-eight hours after removal of the ureteral catheters, and usually without any additional colic.

Ureteral spirals, forceps and rubber bags did not aid in the treatment in these cases. There was no mortality in the series.

*Transplantation.*—Furniss<sup>33</sup> described a technic of uretero-intestinal anastomosis which combined the best features of the Coffey method and certain of his own modifications. Spinal anesthesia is the most satisfactory. A median low abdominal incision is made, and the small intestines are displaced from the pelvis. The sigmoid is clamped just above the sacral promontory. A sigmoidoscope is introduced into the rectum, which under manual guidance is pushed about 7.5 cm. above the anus. The obturator is withdrawn, and through the sigmoidoscope a colon tube is passed to the clamped intestine. The lower part of the intestine is irrigated with saline solution until the fluid returning through the sigmoidoscope is clear; then 500 cc. of 1 per cent mercurochrome-220 soluble is run through. To dissect the ureter from its bed, an incision is made through the peritoneum close to its outer border, and extended downward to the point at which the ureter is divided. The ureter is clamped doubly and divided between the clamps. It is then freed from below upward, an attempt being made to retain the peritoneal attachment by dividing the peritoneum along its inner side. The distal segment of the ureter is ligated with number 1 chromic catgut to prevent bleeding and possible backflow of urine from the bladder. A ureteral catheter is inserted in the ureter after the clamp is removed, and the ureter is tied to it so that the tie falls between these ridges. A small, truncated hollow metal cone is passed over the catheter and slipped up over the tied end of the ureter to facilitate its passage into the intestine at a subsequent stage of the operation. A pointed trocar is screwed to the distal end of the catheter.

The point of implantation is selected. The sigmoidoscope is passed upward beyond this, and with the left hand the intestine is held firmly over it. An incision about 6 cm. long is made to the mucosa. The sigmoidoscope is then manipulated so that the lower end of the incision

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33. Furniss, H. D.: Uretero-Intestinal Anastomosis: A Simplification of the Coffey Technique, *Am. J. Surg.* **15**:12 (Jan.) 1932.

is drawn taut over its lumen. The trocar is plunged through the mucosa into the sigmoidoscope, and passed downward through it; by pulling on the catheter the ureter is drawn into the intestinal canal. The muscularis and peritoneum are sutured over the ureter; portions of the periureteral sheath are included in the suturing to prevent displacement. The peritoneal wound from which the ureter was dissected is closed with catgut. Unless there has been gross soiling, drainage is not necessary.

Walters<sup>34</sup> summarized the results of ureterosigmoidal transplantations in 76 cases in which the ureters were transplanted one at a time without the use of ureteral catheters during the last seventeen years at the Mayo Clinic. If this procedure is performed in the presence of a satisfactorily functioning rectal sphincter, the patient will be able to retain the urine in the rectum, on an average, from two to four hours during the day and from three to five hours at night; this was true in the 59 cases of the series in which the patients were traced and are known to be living. In 30 (50 per cent) of the 59 cases there has been no evidence of renal infection. In 13 cases (21 per cent) there has been slight evidence of mild renal infection at long intervals. Twenty-seven patients have lived more than five years since operation, and 13 have lived ten years. Three (3.9 per cent) of the 76 patients died in the hospital following operation. Twenty were between the ages of 5 and 9 years; 40 were less than 14 years of age, and 17 were between the ages of 15 and 34 years. It is not advisable to perform ureteral transplantation on children until they have gained good rectal control of fecal material, usually after the age of 3 years.

The method of transplantation described by C. H. Mayo was used in all of these cases. The right ureter is transplanted into the rectosigmoid in the first operation, its distal end being carried approximately 2.5 cm. in a trough made by a longitudinal incision along one of the longitudinal bands of the rectosigmoid, through the serosa and the muscle layers of the bowel, and brought down to, but not through, the mucous membrane. Lateral separation of these structures furnishes a trough. A small puncture is made in the mucous membrane at the lower end of the incision to allow the passage of the ureter. A curved needle carrying number 0 catgut is then passed through the open end of the ureter and tied to it. The short end of the catgut is guided into the open end of the ureter for 5 or 6 cm. to insure that the ureter remains patulous during the early days of edema following its transplantation. A curved needle is passed through the opening in the mucous membrane to emerge 1.5 cm. below the incision, drawing the

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34. Walters, Waltman: Transplantation of Ureters to Rectosigmoid and Cystectomy for Exstrophy of Bladder: Report of 76 Cases, *Am. J. Surg.* **15**:15 (Jan.) 1932.

ureter into the lumen of the bowel where the catgut is tied. The divided peritoneum and muscles of the intestine are sutured over the ureter with two rows of catgut. Two or three additional sutures should be used to fix the bowel to the peritoneum to cover and to avoid kinking the ureter and to avoid traction on it. From ten to fourteen days later the left ureter is transplanted into the rectosigmoid. This allows sufficient time for the previously transplanted ureter to function and for any mild symptoms of pyelonephritis which may occur to subside.

The mechanism preventing reflux of liquid feces and gas from the rectosigmoid up the ureters, which would produce pyelonephritis, has been the formation of a valve at the distal 2.5 cm. of the ureter by carrying it between the mucous membrane and the muscularis mucosae of the rectosigmoid.

[COMPILERS' NOTE.—The advances made by Coffey, C. H. Mayo, Walters and others during the last few years in transplanting the ureters into the sigmoid are noteworthy. Numerous technical modifications of the original Coffey-Mayo technic have been made by Coffey, Kerwin, Furniss and others. Walters' article is interesting in that it reports the end-results in a large series of cases from one clinic. Certainly the results at this clinic are excellent and promising for future development of this ideal method of diverting the urinary stream from its normal channels.]

Baidin<sup>35</sup> concluded that the ureter is most frequently injured during gynecologic procedures and at childbirth. Consequently surgery of the ureter is of especial interest to the gynecologist. Heteroplastic or homoplastic replacements of resected ureters by transplants of blood vessels, as well as autoplasmic covering of extensive urinary defects with the peritoneum, are not possible. The method of ureterocholecystostomy, which eliminates the urinary bladder as a carrier of urine, is not satisfactory; neither is uretero-uterocystostomy, as the transplanted section of the uterus is able to function only a short time as a carrier of urine. In most cases in which extensive resection of the ureter and bladder is done, the best results are obtained by a plastic operation, utilizing portions of the ureter, uterus and bladder.

#### BLADDER

*Tumors.*—Joseph<sup>36</sup> has treated 172 patients with tumor of the bladder since 1918, classifying the growths as follows: 59 papillomas.

35. Baidin, Alexander: Ueber Harnleiterplastik und Harnleiterimplantation. *Ztschr. f. urol. Chir.* **33**:363 (Dec. 11) 1931.

36. Joseph, Eugen: Erfahrungen in der Erkenntnis und Behandlung der Blasen-  
geschwülste, *Fortschr. d. Therap.* **7**:242, 1931; abstr., *Am. J. Cancer* **16**:203  
(Jan.) 1932.

42 papillary carcinomas, 69 carcinomas, 1 sarcoma and 1 myosarcoma. It is his belief that many of these cases were a result of aniline irritation, which not only occurred among aniline workers but possibly had their origin in the habitual use of certain cosmetics. Treatment of tumors of the bladder should be conservative. All of his patients were treated primarily with trichloroacetic acid or with actual cautery. Operation is undertaken only when necessitated by hemorrhage or infection, or to secure further palliation and extension of life.

Mathews<sup>37</sup> stated that for clinical purposes tumors of the bladder may be divided into three groups: those projecting well into the bladder and being either papillomatous or pedunculated; sessile growths projecting less into the bladder, spreading laterally along the mucosa of the bladder, with a surface height varying from 1 mm. to 3 cm., and infiltrating growths which invade every layer of the bladder and also surrounding bladder tissue. After a survey of the treatment in 50 cases of tumor of the bladder, both benign and malignant, the following conclusions were made:

Radical excision of the growth as generally performed is not the method of choice. The high frequency current, through the cystoscope or by open operation, when vigorously applied, even in apparently hopeless cases, has worked well. The introduction of cautery and high frequency for excisions and resections was an advance in the treatment of neoplasms of the bladder. Radium in the form of radon seeds, used in conjunction with other types of treatment, has given satisfactory results. Fulguration with the bipolar high frequency current is the method of choice for benign growths, as well as for excision or resection of other types of growth.

If possible, malignant growths should be resected; if not, the high frequency current should be used for excision. If they are not excisable, direct fulguration with high frequency current or cautery may be performed. Radical treatment of malignant growths of the bladder, particularly those that are invasive and ulcerative, tends to aggravate the condition. Palliative treatment should be given with deep roentgen rays for relief of symptoms, and finally suprapubic cystotomy should be done. For benign papilloma, treatment is application of the high frequency current. Multiplicity of tumors usually requires open operation with application of the cautery or high frequency current. Fulguration through the cystoscope in these cases is not practical.

Deep roentgenotherapy may be used as an aid to other types of treatment. It is only palliative and simply relieves pain. Inoperable

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37. Mathews, R. F.: Bladder Tumor: A Survey of Fifty Cases, *Am. J. Surg.* **11**:343 (Feb.) 1931.

carcinoma of the bladder and prostate gland may be treated in this way. It relieves the pain of metastasis; whether it has any curative value is problematic.

Colston<sup>38</sup> stated that before considering any treatment of tumor of the bladder, the presence or absence of infiltration should be determined as accurately as possible. Noninfiltrating tumors are best treated by a combination of endovesical electrotherapy and direct application of radium. By direct application of radium, resistant tumors can usually be made to respond promptly to the high frequency spark, and the possibility of recurrence is markedly diminished. Infiltrating tumors of the bladder should be treated by resection if this procedure can be performed safely. If resection is impossible, the tumor should be destroyed by diathermy through the open bladder and radon seeds implanted throughout its base.

*Stone.*—Luys<sup>39</sup> reported 2 cases of unusually large stones in the bladder. In 1 case, that of a man aged 28, the calculus was removed through a suprapubic incision. It weighed 133 Gm. and was 17 cm. in circumference. The second case was of a man aged 66, who had had severe dysuria and other urinary symptoms for seven years. This stone was removed also through a suprapubic incision, weighed 128 Gm. and was 18 cm. in circumference. A satisfactory result was obtained in each case.

*Diverticula.*—Mariani and Astraldi<sup>40</sup> reported a case in which a hernia of the bladder in the scrotum caused a large diverticulum, with which it was connected by a long neck. Two smaller diverticula developed from this main structure, as shown by cystogram. The strangulation of an irreducible inguinal hernia made an emergency operation necessary. During the intervention a hernia of paraperitoneal type, surrounded by a mass of fat (lipocèle), was encountered; this was the herniated bladder. Histologic examination disclosed a muscular layer which presented the typical appearance of a congenital diverticulum; the lipocèle was the result of the slipping which produced it. On this vesical hernia a secondary diverticulum of the bladder had gradually opened, as was revealed both by cystography and operation.

Any condition capable of producing urinary retention may favor the production of a vesical hernia. If the abdominal wall is soft and flabby and lacks resistance, its fibrous rings may yield to the pressure of the distended urinary reservoir, which slips through and produces

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38. Colston, J. A. C.: The Treatment of Tumors of the Bladder. *Am. J. Roentgenol.* **25**:375 (March) 1931.

39. Luys, Georges: Deux gros calculs vésicaux, *Bull. et mém. Soc. de chirurgiens de Paris* **23**:653 (Nov. 20) 1931.

40. Mariani, B., and Astraldi, A.: Grand diverticule de la vessie logé dans le scrotum, *Arch. urol. de clin. de Necker* **7**:175 (Dec.) 1931.



hernia. It should also be borne in mind that every inguinal hernia constitutes predisposition to hernia of the bladder. The thinning of the walls of the bladder, as well as the loss of contractility, likewise constitutes predisposition to hernia of the bladder.

[COMPILERS' NOTE.—Diverticulitis of the urinary bladder must be distinguished from hernia of the bladder, which appears to be rather common. In reporting 54 cases of the former in 1928, Lowsley and Gutierrez found 15 cases in which the diverticulum was discovered at operation to be adherent to the hernial sac. In 1 of these cases the congenital condition was bilateral and each sac was lying in the scrotum. The case which Mariani and Astraldi present is of interest because the condition was suspected and was diagnosed cystographically before operation. It is important to know that in any type of inguinal, crural or femoral hernia, a urinary fistula may follow as a sequel of an operation for the condition. Hence, in every case of inguinal hernia the possibility of hernia of the bladder should be borne in mind, and in order to obviate this common complication of urinary fistula, the routine procedure of taking cystograms should be considered.]

*Exstrophy.*—Foulds and Robinson<sup>41</sup> stated that until the development of the technic of ureterorectoneostomy, the treatment of exstrophy of the bladder was difficult and the results of treatment unsatisfactory. After Simons' unsuccessful attempt to transplant the ureters into the bowel in 1851, little progress was made until Maydl's work in 1896. The high mortality of this transperitoneal method led Peters, in 1899, to attempt bilateral extraperitoneal transplantation, using catheters to splint the anastomosis and drain the ureters. After insertion of the catheters through the bladder, and their fixation in the ureters by a suture, the ureters with a small area of vesical wall from around the ureterovesical opening were freed extraperitoneally as high as possible. The bladder was then removed, the rectum was exposed below the peritoneal reflection, and the ureters were drawn into the rectum by forceps inserted through the anus. The catheters came away easily after three or four days.

Starr, in 1908, reported that in Peters' 5 cases 4 patients were alive and well, nine, seven, six and five years after operation, and presented 1 of his own cases in which the patient was still alive and well in 1930.

Foulds and Robinson found that 1 of Peters' original patients lived in good health for twenty-six years and died of extravasation of urine and sepsis following rupture of the left ureter incident to the passage of a calculus.

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41. Foulds, G. S., and Robinson, T. A.: The Late Results of the Peters Operation for Exstrophy of the Bladder, *Brit. J. Urol.* 4:20 (March) 1932.

*Cystostomy.*—Marion<sup>42</sup> stated that pain following cystostomy is abnormal and examination should be made to reveal its cause. If carcinoma of the prostate gland exists, the pain is due not to the cystostomy but to the carcinoma. In such cases sedatives are the only possible treatment. If pain persists after cystostomy for hypertrophy of the prostate gland, it may be due to unsatisfactory functioning of the tube in the incision. If the tube is not changed often enough, its lumen becomes partly obstructed by incrustations of urinary salts, causing the bladder to contract painfully to expel urine. The tip of the tube may have such an incrustation, causing it to become a sort of intravesical calculus. Sometimes an elbowed Pezzer catheter does not penetrate into the bladder, but stops short of the deep vesical orifice, which may have retracted and may offer resistance. Pain is then due either to irritation of the sensitive tissues in which the catheter lies or to the contractions that the bladder is forced to make. If the elbowed portion of the catheter is too long, its tip will be in the middle of the bladder, where it will rub the walls and produce irritation. This can be remedied by shortening its length. Pain is often due to vesical calculi if there are no other reasons to account for its existence. Exploration of the bladder with a hystrometer will generally reveal the presence of rough calculous masses if these are present. Under epidural and local anesthesia the abdominal wall should be opened below the cystostomy, a digital examination made, and the calculi removed.

MacGowan<sup>43</sup> and Parker described their operation for suprapubic cystotomy. A transverse incision, about 10 cm. long, is made 3 cm. above the pubic crest, exposing the fascia of the recti muscles. The fascia is incised transversely for about the same length. The muscles are then separated and retracted to each side, which exposes the peritoneal fold. This is dissected off with gauze, care being taken not to expose the cellular tissues around the bladder. The bladder is then grasped with an Allis forceps and an anchor suture is placed. This enters the fascia from the lower median line point and proceeds through the right rectus muscle, then through the detrusor without entering the mucosa, emerging through the margin of the left rectus muscle and lastly through the fascia, where it is tied. A traction suture is placed on each side of the Allis forceps in the wall of the bladder, and the bladder is incised down to the mucosa which is easily penetrated. A Pezzer catheter is inserted through the opening and sutured with an ordinary purse-string suture. The fascia is closed by means of interrupted sutures and the incision in the skin is usually left open.

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42. Marion, G.: Des douleurs après la cystotomie, *J. d'uro.* **33**:160 (Feb.) 1932.

43. MacGowan, Granville: MacGowan and Parker's Operation for Suprapubic Cystotomy, *J. Urol.* **26**:619 (Nov.) 1931.

*Function.*—Dragonas<sup>44</sup> stated that the trigone, which has been regarded by certain authors as the dilator muscle of the neck of the bladder, cannot perform this action because of its anatomic structure and the mechanical conditions under which it acts. The dilator of the neck of the bladder is the external longitudinal layer, particularly the posterior longitudinal band. The latter draws backward the posterior segment of the neck of the bladder, and the anterior group fixes its anterior segment. Although the contents of the bladder play a part in opening the neck, its hydraulic pressure can only be the direct result of the contraction of the muscle of the bladder. The hydraulic pressure, which develops through the effort of the abdomen, can act only under certain conditions. In normal urination these conditions are brought about by the contraction of the muscle of the bladder. The entire phenomenon is intimately related to the contractility of the muscle, which has the capacity for responding to all the claims of the mechanics of the organ. As soon as the dynamic force is changed, the mechanics also undergo alterations. The bladder is not an organ in which mechanical laws are executed according to their own will, as in an inert organ; it utilizes the laws of mechanics, which it directs according to its need.

McCaughan, Major and Braasch<sup>45</sup> stated that it was hoped that cystometry, as devised by Rose, would provide an accurate method of diagnosing cord bladders. Their difficulty of interpreting many of the cystometric curves and of correlating the neurologic and cystoscopic data made it seem improbable that cystometry possessed any notable advantages over cystoscopy. A clinical study was made to show the degree of correlation between results obtained from cystoscopic data as compared with those from cystometric examination. The conclusions as to the comparative advantages of cystometry were that it is only occasionally of positive value without other corroborative data, either clinical or cystoscopic, and its greatest value will probably be in giving additional data in cases in which cystoscopic observations are doubtful.

*Bladder Pain.*—Epstein and Ovtshinnikov<sup>46</sup> stated that the urologist is consulted by many women because of frequency and difficulty of urination and an uncomfortable feeling at the end of urination. The

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44. Dragonas, Eustache: A Study of the Functioning of the Musculature of the Bladder and the Mechanism of Opening of the Neck in Normal Micturition, *Arch. urol. de clin. de Necker* 7:17 (Jan.) 1931.

45. McCaughan, J. M.; Major, S. G., and Braasch, W. F.: Value of the Rose Cystometer in the Diagnosis of Neurogenic Affections of the Urinary Bladder in Man, *J. Urol.* 27:229 (Feb.) 1932.

46. Epstein, I., and Ovtshinnikov, N.: Zur Pathogenese der weiblichen Cyst-algie bei reinem Harn, *Ztschr. f. urol. Chir.* 31:231 (March) 1931.

urine in such cases is usually sterile. Bierhof and Heymann found that 20 per cent of all patients at the Polyklinik had urinary disturbances, while Hoffmann stated that 50 per cent of all gynecologic patients have trouble in the urinary tract. Marion designated the condition as cystalgia. Before cystoscopy the condition was known as irritable bladder, cystospasm, neurosis and neuralgia vesicae. After the cystoscope came into use, inflammatory changes of various degrees of the trigone and vesical neck, loosening, desquamation and cloudy swelling of the epithelium of the trigone and, at times, polyps at the vesical neck were observed. The lesion was then called cystitis colli, trigonitis, cystitis trigoni, cystitis colli papillaris and cystitis proliferans. The lack of pathologic elements in the urine is explained by the fact that inflammatory elements in chronic cystitis are only sparsely exhibited and tend to show themselves in the deeper layers of the mucous membrane.

This condition and its pathologic anatomy has not been emphasized in the literature. Heymann, in 1905, examined the bladders of 20 women, 5 men and 5 children, none of whom had a history of urinary infection. In 19 of the 20 women examination revealed pathologic changes in the regions of the trigone and sphincter, subepithelial infiltration in 6 cases and deep epithelial changes in the form of metaplasia and cystitis cystica in 13 cases. Examinations of the men and the children gave entirely negative results. In 1923 Maeda examined the bladders of 71 female cadavers and found changes in the trigonal epithelium in all.

Two factors are significant in this condition: circulatory disturbances of the pelvis and infection. Many observers have considered a relationship to various associated conditions. Zuckerkandl mentioned pelvic circulatory disturbances with trigonal hyperemia and close proximity to the uterine cervix; Knorr, the association of cystocele and similar pelvic lesions causing stasis; Winter and Stoeckel, its relation to pregnancy and postpartum factors; Zangenmeister, uterine myomas, and Choltzov, gonorrhea. To this extensive group may be added nervous disturbances preceding disease of the spinal column, vasomotor hyperesthesia, constitutionally increased sensitiveness of the bladder, polyps and erosions of the external genitalia, stenosis of the external urinary orifice, intraperitoneal tumors, ureteral kinking, rectal diseases and a "habit bladder." In 781 cases of urinary disturbances of women, 166 cases (21.3 per cent) showed clear urine and occurred between the ages of 20 and 50 years. In 10 per cent of cases gonorrhea was present, in 17 per cent possibly previous cystitis and in 2 per cent pyelitis. In 82 of 113 cases some type of gynecologic disorder was associated with the cystalgia. Numerous bacteriologic studies of the urine and histologic examinations of the trigone revealed evidences of chronic infection.

It was concluded that for an anatomic basis of cystalgia in women, chronic infection of the vesical neck is present and probably dependent on the physiologic circulation of the blood in the pelvis. The authors did not conclude that bacteriuria is of any significance.

#### PROSTATE GLAND

*Hypertrophy.*—Vernet<sup>47</sup> described a new method of prostatectomy called "pararectal." The hypogastric method causes much suffering, and there are a great many inherent difficulties in the classic perineal method. Three spaces where tissues could be separated have been confirmed by examination of cadavers. These are between the prostate gland and the "prostato-perineal aponeurosis," between this aponeurosis and the anterior aspect of the rectum and between the longitudinal fibers of the rectum and the layer of circular fibers. Removing in one mass the prostate gland and the rectum and bladder, which are fixed in a diluted solution of formaldehyde, an incision with scissors is made in the rectum from bottom to top by the middle of the posterior wall, so that the rectal walls could be spread out; the incision is then carried through the center of the rectum, prostate gland and bladder, dividing the mass into two symmetrical halves. This reveals the spaces between the prostate gland and the rectum. Another consideration in the pararectal route is the incision of the knot of the perineum. The usual method approaches this obstacle blindly, and the rectum or external sphincter is likely to be injured. This difficult point is eliminated by the pararectal routes. With the left index finger introduced into the rectum as a landmark, the blunt point scissors, having sectioned the anobulbar raphe, continues to cut in front of the internal sphincter of the anus until the knot of the perineum is reached; this appears at the bottom of the wound in the form of a whitish tract, and is recognized by the finger as a resistant bridle, which must be cut. The space described must be separated either by blunt dissection or by introducing a gauze tampon. The separation is made over an extent of 2 cm., which is sufficient for the insertion of a rectal speculum.

Vernet has used this method in 122 cases, in 102 of which there were adenomas; in 9, abscesses; in 6, vesical calculi, and in 3, carcinomas; in only 1 case was there a rectal fistula.

The explanation of this is as follows: In anatomic dissection it is seen that the portion of the bed of circular fibers that must be separated from the longitudinal fibers corresponds in part to the internal sphincter of the anus; at this level the bed of circular fibers is 5 or 6 mm. thick and serves as a protection to the rectal mucosa at the internal sphincter. This extends from the edge of the anus to the top of the prostate

47. Vernet, S. G.: La prostatectomie para-rectale, J. d'urol. **33**:1 (Jan.) 1932.

gland, so that it passes above the nucleus of the perineum. The result is that the extent of the rectal wall in which the separation of fibers must be made from the circular fibers is not more than 1.5 cm.

In carcinoma of the prostate gland Vernet uses the classic route. The indications for the pararectal route are limited to adenoma of the gland, abscess and stone in the bladder, and the application of radium. By this method the muscle fibers of the rectum are not cut; the muscular beds are simply opened, following the line of cleavage, creating a sheath-shaped space, which disappears after intervention without leaving any dead spaces. This seems to be one of the reasons for the rapid cicatrization which takes place; the perineal wound is closed usually at the end of from twelve to fifteen days, and the patient is able to urinate with perfect ease. No case of urethroperineal fistula has been observed in patients treated by this method. The chief advantage of this method depends on the absolute preservation of the muscles, vessels and nerves of the perineum. Genital functions are not as a rule disturbed, as frequently occurs in the perineal operation. In only the first 3 cases of this series did erections disappear. Sexual potency was diminished in a few cases, but was perfectly conserved in the majority. The impotence following the perineal operation is due not to section of the ejaculatory ducts but to the elongation, section or tearing of the nerves concerned in the erector reflex.

Fullerton,<sup>48</sup> in the treatment of secondary hemorrhage after suprapubic prostatectomy, used a spheric hemostatic rubber bag, which can be made to fit accurately into the prostatic cavity and cannot enter the membranous urethra. One disadvantage of the Pilcher bag is that it enters the membranous urethra and stretches the compressor urethrae muscle, causing temporary or permanent incontinence.

A catheter is first passed into the bladder, preferably a soft rubber one. A light forceps is then introduced through the suprapubic wound. Usually the catheter can be easily seized by the forceps and brought out of the wound; if not it may be necessary to introduce the finger to locate it. The urethral tube of the hemostatic bag is then pushed over the end of the catheter and both are ligated. The tube and bag are then smeared thickly with sterile lubricant to facilitate withdrawal of the urethral tube and to prevent the bag from becoming too embedded. The catheter is then withdrawn through the ureter, bringing the bag, which is thin and collapsible, into position. The bag is then distended by filling it with water, so that it bulges over the edges of the prostatic cavity and makes contact with the walls of the latter; thus pressure can be exerted on both by light traction at the urethral end. The pressure

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48. Fullerton, Andrew: The Treatment of Secondary Haemorrhage After Suprapubic Prostatectomy, *Brit. M. J.* 2:1078 (Dec. 12) 1931.

is maintained by attaching a weight to the tube from the urethra by a piece of cord, which can be brought over the foot of the bed. The bag must not be overdistended, or it will not fit snugly into the prostatic cavity but press on the base of the bladder and may even exert injurious pressure on the ureteral orifices. The bag is kept in position for two or three days, and should not be removed until the danger of hemorrhage has ceased. It may be allowed to collapse and remain in the bladder as a precautionary measure. In the meantime the urethra is irrigated by the side of the tube, using any suitable antiseptic solution, to reduce the risk of urethritis from the presence of a foreign body. The bag may be removed easily through the suprapubic wound. To prevent infecting the bladder by drawing the exposed part of the urethral tube back through the urethra, the bag may be cut off close to the meatus before removal.

*Carcinoma.*—Walthard<sup>49</sup> described 2 cases of squamous cell carcinoma of the prostate gland. One of these tumors disclosed undifferentiated, solid cell groups, many undifferentiated and some differentiated squamous cells and also bands of cells containing lumens. It was not certain that the squamous cells were the result of a fetal deposit; consequently the diagnosis could not be absolute.

Squamous cell carcinoma in the prostate gland arises on the basis of chronic inflammation, either as a metaplastic change from leukoplakia or through metaplasia from undifferentiated tumor cells to squamous cells. The squamous cell growth, as well as an associated leukoplakia, did not arise from the so-called basal cells but from the middle cell layer, the tumor cells probably regenerating from the cubical cells of the gland to cylindric cell formation. The formation of the squamous cell carcinoma has no definite relationship to adenoma of the prostate gland.

*Abscess.*—Sargent and Irwin<sup>50</sup> reported 42 cases of abscess of the prostate gland. They concluded that in any acute inflammation of the prostate gland there is no danger in delaying until a definite diagnosis may be made of frank formation of abscess. Both prostatic lobes should be opened, whether or not the signs indicate bilateral formation of abscess. There is an unnecessary risk of persisting urethritis from false cavity formation in any method of treatment which involves opening of the abscess into the posterior urethra. Drainage through external urethrotomy prolongs morbidity, favors the development of complicating epididymitis, and entails the risk of a more or less persistent

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49. Walthard, B.: Zur Genese der Plattenepithelkrebse der Prostata, Ztschr. f. urol. Chir. **32**:411 (July 22) 1931.

50. Sargent, J. C., and Irwin, Robert: Prostatic Abscess: A Clinical Study of 42 Cases, Am. J. Surg. **11**:334 (Feb.) 1931.

urinary fistula. Radical perineal dissection with posterior prostatomy is the method which offers the best possibility of cure and more freedom from complications.

#### URETHRA

*Obstruction.*—Frontz<sup>51</sup> stated that three types of valve formations in the posterior part of the urethra have been described. In the first, most common type, there is a ridge on the floor of the urethra continuous with the verumontanum, which takes an anterior course and divides forklike into two processes which are inserted into the urethral wall in the region of the bulbomembranous juncture. These processes are continued as thin membranous sheets directed upward and forward which may be attached to the urethra throughout its entire circumference. In the second type there exists a condition similar to the first type, except that the ridge passes from the verumontanum toward the internal sphincter, just outside of which it divides forklike into two processes which are continued as membranous sheets and attached to the wall of the urethra. The third type may be found at any level between the two sphincters. Jarjavay described it as an iris valve because of its similarity in shape to the iris of the eye. The most common variations of this type are more or less crescentic or semilunar folds which cross the urethra transversely or vertically.

Three cases are reported in which the urinary obstructions, although probably congenital in origin, differed markedly from the three types originally described by Frontz and others.

*Rupture.*—Smith and Mintz<sup>52</sup> reported 30 cases of traumatic rupture of the urethra, 13 of which were complicated by fractures of the pelvis. Two of the 13 patients were not operated on; 1 of these died; suprapubic exploration but not cystotomy was performed on 2, both of whom died, and suprapubic cystotomy was performed on 9 with 5 deaths, a mortality of 61.5 per cent. Of the 17 cases not complicated by fractures, there was no operation in 2; preliminary cystotomy with later repair of the urethra was done in 2; perineal section with suture of the divided urethra, in 7, and perineal section without suture of the urethra, in 6. There was 1 death (6 per cent). Simple ruptures of the bulbous urethra caused by blows on the perineum can usually be repaired by perineal operation without suprapubic cystotomy. Cases complicated by fracture of the pelvis, in which there is considerable perivesical bleeding, should be treated by suprapubic cystotomy.

51. Frontz, W. A.: Congenital Urinary Obstructions in Male Children, with Reports of Cases Presenting Unusual Anomalies, *J. Urol.* **27**:489 (April) 1932.

52. Smith, G. G., and Mintz, E. R.: Rupture of the Male Urethra, *New England J. Med.* **205**:421 (Aug. 27) 1931.



*Fistula.*—Davis<sup>53</sup> reported that the spontaneous closure of 3 fresh urethrorectal fistulas was accomplished by means of continuous gentle aspiration of the urine through both a suprapubic tube and a urethral catheter. Suprapubic urinary aspiration was done by an apparatus whereby siphon flow is indefinitely maintained by means of a simple mercury manometer, which automatically maintains the air pressure in the urine jug at a constant level. When treatment was begun, a functionless internal vesical sphincter and gross fecal drainage through the suprapubic fistula, as well as urinary and fecal drainage through the perineum, were present in each case.

#### PENIS

*Carcinoma.*—Wolbarst<sup>54</sup> stated that the morbidity rate of carcinoma of the penis is at least 2 per cent of all carcinomas among male patients in the United States. Phimosis is generally recognized as the most significant factor in the etiology of this lesion. Circumcision in adult life or adolescence does not protect completely against future malignancy because of the injury to tissue already affected. Chronic balanitis in middle-aged or elderly men should always be regarded as potentially malignant.

Staff physicians of 205 American hospitals and 6 individual observers reported 1,103 cases of carcinoma of the penis in the United States; none occurred in Jews. From 26 Jewish hospitals there were no cases reported among Jews. A total of 2,484 penile carcinomas were reported in uncircumcised men, and 33 occurred in circumcised Mohammedans. Not a single case was reported as occurring in a circumcised Jew. The immunity against carcinoma of the penis among Jews and Mohammedans is not racial, but is provided by the practice of circumcision in early life. Wolbarst is of the opinion that at least 225 deaths annually in the United States and 150 in England and Wales and probably twice as many nonfatal cases can be prevented by the circumcision of all male children in infancy.

[COMPILERS' NOTE.—There is every evidence to support the belief that irritation from a phimotic prepuce predisposes to carcinoma of the penis. Unquestionably the factor of irritability can be prevented almost entirely by circumcision. If this procedure were carried out universally in infancy, carcinoma of the penis would probably become a pathologic curiosity.]

53. Davis, Edwin: The Spontaneous Closure of Fresh Urethrorectal Fistula: Report of Three Cases, with Presentation of a Manometer Suprapubic Urinary Drainage Apparatus, J. A. M. A. **98**:1542 (April 30) 1932.

54. Wolbarst, A. L.: Circumcision and Penile Cancer, Lancet **1**:150 (Jan. 16) 1932.

## INFECTIONS OF URINARY TRACT

Young, Colston and Hill <sup>55</sup> stated that the bacteriology of the urinary tract shows varied flora and organisms of a wide range of virulence and susceptibility to antiseptics. The colon bacillus is inhibited by 1:500,000 corrosive mercuric chloride, whereas *Bacillus lactis-aerogenes* is not inhibited until the strength of chloride in the broth culture is 1:30,000. The alkalizing bacteria are best combated by acids. The use of chemotherapy and protein therapy are of value.

Bacillary infections of the urinary tract, particularly the *Aerobacter* group, have been shown to be especially resistant, but some cases have responded satisfactorily to intravenous injections of mercurochrome-220 soluble. Septicemia of urinary origin and sepsis without infection of the blood stream are in some instances benefited by chemotherapy. It is advisable to supplement local injections and irrigations in urinary infections with intravenous treatment. Neoarsphenamine and mercurochrome-220 soluble have been found to be effective when given intravenously.

[COMPILERS' NOTE.—Young and his associates have contributed much to the knowledge of the bacteriology of infection of the urinary tract. In spite of the fact that this advocacy of chemotherapy, especially with intravenous injections of mercurochrome-220 soluble has varied in popularity from time to time, many strikingly good results have been obtained by this procedure. Although it is not a specific for urosepsis, as it was hoped it would be at the time of its introduction, nevertheless after ten years its originator still maintains that it has a place in treatment, and this contention finds numerous supporters. Neoarsphenamine also seems to have advocates, not to speak of the numerous azopyridine dyes which find their place in the drug market from time to time. Each of these chemicals appears to exert an excellent effect in helping to keep down infection of the urinary tract in certain instances, but each fails in many instances. We have as yet to find the ideal antiseptic for the urinary tract.]

Nesbit <sup>56</sup> stated that acute staphylococcal infections of the kidney are relatively common. They are hematogenous in origin, a definite focus generally being present. The lesion in the parenchyma is usually cortical, and shows a marked tendency to heal promptly and completely. There are always costovertebral pain and tenderness. Stained urinary sediment should be examined in all suspected cases. The disease tends

55. Young, H. H.; Colston, J. A. C., and Hill, J. H.: Infections in the Genito-Urinary Tract, and Complications; Further Advances in the Treatment, *J. A. M. A.* 98:715 (Feb. 27) 1932.

56. Nesbit, R. M.: Acute Staphylococcal Infections of the Kidney; Their Clinical Aspects and Treatment, *J. A. M. A.* 98:709 (Feb. 27) 1932.

to run a stormy though self-limiting course, ending in complete recovery in the majority of cases. If complications develop, perinephric abscess being the most common, surgical intervention should be employed.

Kennedy<sup>57</sup> stated that the colon bacillus is the usual infecting organism in the urinary tracts of children who have pyelitis. Four cases of children who died unusually early after the infection are reported, together with histologic studies. In each instance infection of the urinary tract was by colon bacilli solely and without accompanying obstruction. There was an acute, widespread, suppurative process involving the renal and peripelvic tissues. In these cases, of several days' to three weeks' duration, there was definite pyelitis, peripelvic inflammation, abscesses and diffuse infiltration of the parenchyma. These lesions showed a tendency to heal promptly.

Hematogenous and ascending lesions, with and without obstruction, were produced experimentally. The hematogenous lesions occurred first in the cortex and medulla, and the ascending lesions appeared first in the pelvis and peripelvic tissues. In both types of infection the process spreads rapidly to the entire kidney, so that, after from forty-eight to seventy-two hours, it may be impossible to ascertain how the lesions were produced. Obstruction did not favor localization in the kidney of organisms injected intravenously. The process of healing began early, as it does in human beings, and proceeded rapidly, with ultimate formation of fibrous tissue.

In every instance, both in human beings and in experimental animals in which early lesions occurred, the pelvis participated in the process.

[COMPILERS' NOTE.—Kennedy's observations are interesting in that experimental hematogenous infections were shown to produce lesions first in the parenchyma of the cortex and medulla, whereas the ascending infections involved the pelvis and peripelvic tissues primarily. In both types, subsequent development of the infection became diffuse, the process spreading to the entire kidney. While it is probably true that stasis is a great factor in promoting and maintaining renal infection, especially in lesions of the ascending type, Kennedy's demonstration that unilateral obstruction of the ureter did not definitely affect the localization and development of hematogenous infection is noteworthy.]

Bazy and Oudard<sup>58</sup> stated that there is undoubtedly such a condition as amicrobic pyuria. It is probable that pyuria and leukocyturia are sometimes permanent, with intermittent passage of germs, which cannot properly be called intermittent amicrobic pyuria. The inter-

57. Kennedy, R. L. J.: The Pathologic Changes in Pyelitis of Children Interpreted on the Basis of Experimental Lesions, *J. Urol.* **27**:371 (April) 1932.

58. Bazy, P., and Oudard, P.: Les pyuries amicrobiennes, *J. d'urol.* **31**:321 (April) 1931.

mittent disappearance of germs would correspond to a process of auto-sterilization, the mechanism of which is not well defined.

Besides amicrobic leukocyturia and pyuria, of mechanical or chemical origin, there are leukocyturia and pyuria of infectious origin in which the micro-organism cannot be practically demonstrated because it rarely passes in the urine, and only indefinitely multiplied researches could ever succeed in finding it. In the present state of knowledge this germ probably is the colon bacillus or a staphylococcus, and would presumably undergo autosterilization, like the preceding type. It may be a totally unknown micro-organism, and one impossible to isolate by any means of examination or culture now in use.

Such pyuria may also be due to a unilateral lesion, which may be termed juxtarenal, but it is more probably parenchymatous. It may be a common microbe, of the colon or staphylococcus variety, harmless until a tuberculous abscess or a syphilitic gumma brings it into activity.

A diagnosis of renal tuberculosis is not warranted in cases of amicrobic pyuria unless confirmed by inoculation of guinea-pigs.

Schultz<sup>59</sup> reported on results of bacteriophage as a therapeutic agent in genito-urinary infections. Of 191 cases analyzed, 40 were acute and subacute cases and 151 were chronic cases.

In the 151 chronic cases 72 patients were reported either cured or definitely improved clinically, while the condition of 79 was considered unchanged or negative. Of the 72 cases, the infection recurred in 15 within ten days, in 1 case after two weeks and in 1 case after three months. In 13 cases the urine apparently was not entirely free of the colon organism at any time, although there was clinical improvement immediately following treatments. Forty-two patients (28 per cent) in the entire series of 151 with chronic infection may be considered both clinically and bacteriologically to have recovered. The condition of 32 of this number cleared within forty-eight hours after the first dose of bacteriophage was administered; the remaining 10 responded within seventy-two hours. In the series of 79 patients who failed to respond to this treatment, associated pathologic conditions were indicated in the diagnosis or clinical histories of a fair proportion.

Of the 40 patients with acute pyelitis and cystitis, 35 (87 per cent) responded promptly, both clinically and bacteriologically, to the bacteriophage, in contrast to the recovery of 28 per cent of those with the chronic condition. Of the 35 patients who responded to treatment, the condition cleared within forty-eight hours in 27, in from forty-eight to seventy-two hours in 6 and between the third and tenth day in 2. Two of the patients had recurrence within ten days.

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59. Schultz, E. W.: Bacteriophage as a Therapeutic Agent in Genito-Urinary Infections, *California & West. Med.* 36:33 (Jan.); 91 (Feb.) 1932.

Schultz concluded that in certain types of infections, bacteriophage, properly chosen and administered, is worthy of trial. Its usefulness is limited not only by the difficulty in procuring suitable bacteriophages for individual cases but, to some extent, also by such obstacles as are offered by bacterial variation.

#### UROGRAPHY

Lanman and Mahoney<sup>60</sup> stated that intravenous urography is a valuable adjunct in the diagnosis of disease of the urinary tract. There are definite limitations of its use for children, and it should not be used generally by the pediatrician who is unfamiliar with urologic procedures or by one unfamiliar with the interpretation of the urograms of young patients. In some cases of congenital anomaly of the urinary tract, intravenous urography alone will establish the diagnosis (double ureter, bilateral polycystic kidneys). In one anomaly, a double bladder, with exstrophy of one bladder and epispadias, the data were not conclusive as to whether there were one, two or more kidneys, nor was there any visualization in the ureters of either of the bladders. In cases of exstrophy of the bladder following transplantation of the ureter, intravenous urograms afforded only fairly good visualization. However, this is the only method at present available for obtaining visualization of the kidneys and ureters in such cases.

In 1 case intravenous urography established the differential diagnosis between new growth of the kidney and new growth of the liver. The procedure is valuable in tuberculosis of the kidney when cystoscopy is not possible on account of cystitis. In cases of urinary calculus, especially if there is obstruction to the outflow of urine, good visualization of the urinary tract is usually obtained by this procedure, eliminating the necessity for retrograde pyelography in many cases. In 1 case it gave definite information that had not been obtained by repeated retrograde pyelography, demonstrating no abnormality at the ureteropelvic juncture or in the upper calix of the kidney. It is pointed out that cases associated with considerable infection of the urinary tract and concomitant renal injury may not afford satisfactory visualization by the use of the urographic mediums injected intravenously. In 234 consecutive cystoscopic examinations it was noted that about 60 per cent of the diseases of the urinary tract of children are associated with varying degrees of pyuria.

Intravenous urography is limited in cases in which there is a marked degree of pyuria associated with injury of the kidney, and this group of cases comprises a large percentage of the disorders of the urinary tract common among young patients. The evidence obtained in many

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60. Lanman, T. H., and Mahoney, P. J.: Intravenous Urography in Infants and in Children, *Am. J. Dis. Child.* **42**:611 (Sept.) 1931.

of these cases is inconclusive and unreliable. The dangers of intravenous urography are presumably slight but must be considered. In cases not associated with marked pyuria, this procedure may often eliminate the need for retrograde pyelography, and may sometimes give additional information when used in conjunction with the latter. Its general use in unselected and not carefully studied cases is to be avoided because of the expense and uncertainty of the information often obtained.

It is the belief of the authors that at present the value of this method of visualization of the urinary tract is in direct proportion to the user's knowledge of diseases of the urinary tract in this age group and to his experience and skill in the technical procedures necessary for the adequate study and treatment of these conditions.

Parker<sup>61</sup> considered the technic and value of taking urethrograms. Proper position of the patient and a suitable opaque medium are essential for success. The patient should be sitting up on the roentgen ray table with his back as straight as possible and his legs extended in front of him. The roentgen ray tube should be centered on the symphysis at an angle of 60 degrees with the table. Fifteen cubic centimeters of heavy iodized poppy seed oil 40 per cent is injected slowly so as not to overdistend the urethra and induce spasm of the sphincter. With this technic valuable information can be obtained as to the position and extent of urethral strictures, false passages, fistulas, diverticula and periurethral abscesses which will serve as a guide in determining the type and extent of surgical procedure for their cure.

Legueu<sup>62</sup> called attention to the significance of the dynamism of the renal pelves and ureters in the genesis of urinary disturbances during the course of various morbid processes. The use of pyeloscopy has opened entire new horizons of pathologic physiology, the existence of which was before unknown. It has shown that ureteral lesions are mainly disturbances of motility and that hydronephrosis, even when it appears to be of a mechanical order, is only a neuromuscular disorder. The varieties and modalities of these movements observed by pyeloscopy are infinite and their combinations innumerable. There are spasms, produced by the iodized solution or made more pronounced by it; retardation of evacuation, when the contractions are slower or less energetic; incontinence, when the flow of urine is without nervous control, and retention of a purely functional nature, without mechanical obstacles. It is the combination of these different dynamic troubles that produces the type of lesion observed. Many strictures of the ureter

61. Parker, Geoffrey: The Uses and Interpretation of the Urethrogram, *Brit. J. Urol.* **4**:1 (March) 1932.

62. Legueu, F.: Le dynamisme en urologie, *J. d'urol.* **31**:6 (Jan.) 1931.

are found to be cases of spasm, and are not organic. In other cases in which there is a true stricture, the dilatation and atrophy of the kidney above it can be explained by the simple mechanical disturbance of the function of nerves and musculature. During the period preceding the dilatation, when the pelvis, still of normal proportions, is harassed only by muscular trouble, which will lead later to dilatation, it is no doubt possible to arrest the later stages of hydronephrosis by suitable therapeutic measures. The etiology of these motor disturbances is still somewhat problematic. The cause may be local, such as traumatism, compression from without or obstruction from within, or it may lie in the composition of the urine. Purely nervous influences may be in question, too complex to be analyzed in the present state of our knowledge. Finally, general influences, such as intoxications and infections may be acting on the musculature.

[COMPILERS' NOTE.—The visualization of the upper part of the urinary tract, which has been possible only since the introduction of pyelography in 1906 by Voelcker and von Lichtenberg, has aroused a constantly increasing interest which reached its climax with the advent of pyeloscopy and intravenous pyelography. These two new methods of examination have been outstanding achievements of medical science in the last decade. Many congenital and acquired lesions of the upper part of the urinary tract which for various technical reasons could not be diagnosed before operation or postmortem examination are today easily discovered by means of these two methods of diagnosis. The Necker school has demonstrated the extent to which pyeloscopy has helped in the study of the physiologic pathology of the peristaltic contractions and various other movements, and in determining the emptying time of the pelvis and the excretory apparatus, which until recently were not considered of any particular significance. The enormous field of silent physiologic and pathologic conditions of the upper part of the urinary tree that has thus been opened to our knowledge gives promise of a better handling of these doubtful cases in the future. It will also be possible to clarify some of the present erroneous conceptions with reference to the nature of slight symptomatic hydronephrosis and the so-called strictures or spasmodic contractions of the lumen of the ureter.]

McKenna<sup>63</sup> stated that intravenous urography is of value in the early diagnosis of trauma of the urogenital tract. Early surgical intervention should be resorted to when indicated, as shock and time are significant factors. Nephrectomy is not always indicated in rupture of the kidney; in many cases good results may be obtained by removing the clots and suturing the kidney. Treatment of a tear of the ureter

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63. McKenna, C. M.: Traumatic Lesions of the Urogenital Tract, *J. Urol.* 27:95 (Jan.) 1932.

may be done by retrograde catheterization, screwing this catheter into one introduced from below.

Intravenous urography in rupture of the bladder will show whether the tear is intraperitoneal or extraperitoneal. In rupture of the urethra two interlocking sounds should be used, one introduced from the bladder through a suprapubic cystotomy, and the other through the meatus, establishing coaptation of the severed ends of the urethra and drainage.

#### UROLOGIC DIAGNOSES

Bourgeois and Gagnon<sup>64</sup> stated that urologic examination should be made in cases of indefinite pain on the right side of the abdomen, particularly with reference to appendicitis and ovaritis, to rule out lesions of the upper part of the urinary tract and to prevent unnecessary operations.

A case is reported of a woman, aged 32, who had had an appendectomy performed fourteen years before and who, two years later, underwent a second exploratory and gynecologic operation for pain on the right side of the abdomen a little above McBurney's point. Ten years subsequent to this, the abdominal pain was still present. The patient also gave a history of having had hematuria and other urinary symptoms. Urologic examination revealed the presence of nephrolithiasis on the right side. The left kidney was functioning normally, but the right one was the site of an old chronic lesion of multiple stones and pyonephrosis. The right kidney was removed.

It has been emphasized repeatedly in current literature that pain on the right side is not always indicative of appendicitis and that in about 35 per cent of all cases of chronic appendicitis in which symptomatic relief is not obtained after operation the offending lesion has been found in the right ureter or the right kidney.

Lehmann<sup>65</sup> reported on a study of spina bifida and its relation to abnormalities of the urinary passages. He concluded that a bony defect of the lower part of the spine and sacrum is occasionally associated with changes in the urinary tract, and cited 2 of his cases to corroborate his belief. In certain cases it is possible that the disturbances of the upper part of the urinary tract may be secondary to a spinal or sacral defect in the same manner that lesions in the central nervous system result from the bony anomaly. His observations, considered from the point of view of modern urology, suggest that some urinary lesions are definite diseases of the system rather than local conditions.

64. Bourgeois, B. G., and Gagnon, O. A.: Errors in the Diagnosis of Lesions of the Right Side of the Abdomen, *Union méd. du Canada* **61**:314 (Feb.) 1932.

65. Lehmann, Ernst: Spina bifida und obere Harnwege, *Ztschr. f. urol. Chir.* **33**:406 (Dec. 11) 1931.



*Granuloma Inguinale*.—Greenwood<sup>66</sup> reported 22 cases of granuloma inguinale which occurred in the Federated Malay States. This condition is widespread through India, Brazil and the Pacific Islands, and it occasionally occurs in the United States. The incubation is indefinite, but the lesion usually appears in from two to eight days, and occurs almost always in the region of the genitalia; it starts as a small nodular thickening, which readily excoriates and forms a friable, easily bleeding ulcer.

Greenwood treated the lesions by fulguration with the patients under general anesthesia. The average time for the ulcer to heal was about seventy days. From the appearance of the condition and follow-up of the cases, the cure is apparently lasting. Greenwood is of the opinion that the Leishman-Donovan body found only in smears from the ulcer is not the causative organism but a nosoparasite.

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66. Greenwood, F. G.: The Treatment of Granuloma Inguinale by Diathermic Fulguration: An Analysis of Twenty-Two Cases, *Brit. J. Radiol.* **4**:488 (Oct.) 1931.

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